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OXTR DNA methylation moderates the developmental calibration of neural reward sensitivity

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Abstract

The Adaptive Calibration Model of Stress Responsivity (ACM) suggests that developmental experiences predictably tune biological systems to meet the demands of the environment. Particularly important is the calibration of reward systems. Using a longitudinal sample ($N = 184$) followed since adolescence, this study models the dimensions of early life stress and their effects on epigenetic modification of the oxytocin receptor gene (*OXTR*) and individual differences in neural response to reward anticipation. We first created a latent variable model of developmental context using measures collected when participants were 13 years old. As adults, two subsets of participants completed a reward anticipation fMRI paradigm ($N = 82$) and agreed to have their blood assayed for (*OXTR*) DNA methylation ($N = 112$) at two CpG sites. Three latent constructs of developmental context emerged: Neighborhood Harshness, Family Harshness, and Abuse and Disorder. Greater *OXTR* DNA methylation at CpG sites −924 and −934 blunted the association between greater Neighborhood Harshness and increased neural activation in caudate in anticipation of rewards. Interaction effects were also found outside of reward-related areas for all three latent constructs. Results indicate an epigenetically derived differential susceptibility model whereby high methylation coincides with decreased association between developmental environment and neural reward anticipation.

KEYWORDS

developmental plasticity, early life stress, neighborhood quality, neural reward, OXTR

1 | INTRODUCTION

The Adaptive Calibration Model (ACM) of Stress Responsivity posits that adult phenotypes arise from individuals calibrating to meet the needs of their developmental context (Ellis, Giudice, Giudice, & Shirtcliff, 2017). Rather than early life stress (ELS) leading to *just* negative outcomes, gene by environment interactions produce biological and behavioral phenotypes that are functional if imperfect. It is from this perspective that we investigated a specific instance of gene by environment interaction, namely, the role of epigenetic modification of the oxytocinergic system in the developmental calibration of neural reward sensitivity. The oxytocin receptor gene is sensitive to developmental context and deeply involved in regulating neural reward systems (Love, 2014), which in turn are highly implicated in learning, motivation, mood, and psychopathology (Luking, Pagliaccio, Luby, & Barch, 2016). Understanding the unique interaction between dimensions of developmental adversity, *OXTR* epigenetic modification, and adult neural reward sensitivity can help us understand normative responses to developmental stressors. Importantly, the current study is translational, and taken from the prairie vole (*Microtus ochrogaster*) model system which supplies us with the necessary functional connections between ELS, DNA methylation, gene expression, and calibration of neural reward regions, to enact our study design.

1.1 | Dimensions of early life stress and calibration of reward systems

Amassing research suggests ELS has a profound impact on individual differences from behavior to neurons (Fareri & Tottenham, 2016; Miller, Chen, & Parker, 2011; Wadsworth, Evans, Grant, Carter, & Duffy, 2016). However, the construct of ELS is not well defined. The dominant model of ELS is to characterize varied stressors from parental abandonment to resource scarcity as additive and create a cumulative risk factor which in turn compromises development and health. However, newer models, such as ACM, espouse a dimensional approach (Ellis, Figueredo, Brumbach, & Schlomer, 2009b; McLaughlin, Sheridan, & Lambert, 2014). Life History Theory, the foundation of ACM, separates developmental context into two dimensions: Harshness and Instability. Because bioenergetic resources are finite, the body in development takes its cues from the environment to determine what biological processes should be invested in and when. ACM predicts that children who develop in unreliable environments will calibrate towards less risk-adverse, more reward sensitive, and more impulsive adult phenotypes (Belsky, Steinberg, & Draper, 1991; Ellis, Figueredo, Brumbach, & Schlomer, 2009a). Accordingly higher Harshness and Instability should favor conditional adaptations that enhance neural systems supporting reward-motivation (Figueredo et al., 2006). Specifically, orbital frontal cortex (OFC) and striatum, especially the subregions of nucleus accumbens (NAcc) and caudate, should be implicated as these regions have all been implicated in the anticipation and receipt of reward, creating a putative motivational "reward system" (Liu, Hairston, Schrier, & Fan, 2011; Robbins & Everitt, 1996).

ACM is new, but support for its predictions can be found at the behavioral and neural levels. Behaviorally, the research indicates that children from lower SES families (high harshness) will discount bigger delayed rewards (Sturge-Apple et al., 2016) and even children from high SES will do this in the presence of an unreliable (high instability) adult (Michaelson, de la Vega, Chatham, & Munakata, 2013). Children with hawkish (faster life history trait) tendencies will also show enhanced problem solving for rewards (Suor, Sturge-Apple, Davies, & Cicchetti, 2017). At the neural level, research indicates that the striatum is sensitive to childhood experiences of harshness: abuse and neglect (Hanson, Hariri, & Williamson, 2015), low economic privilege (Cavanagh et al., 2013; Gonzalez, Allen, & Coan, 2016; Gonzalez, Puglia, Morris, & Connelly, 2017; Hanson et al., 2015), childhood social economic status (Cavanagh et al., 2013), and relative status (Ly, Haynes, Barter, Weinberger, & Zink, 2011). The impact of ELS on reward systems are not always in the expected ACM direction of increased reward-related response (perhaps due to the nebulous construct of ELS itself). However, in line with ACM, a recent meta-analysis of fMRI data indicates that lower SES is associated with structural and functional upregulation of reward-related regions including caudate and OFC (Yaple & Yu, 2020).

1.2 | Developmental calibration of *OXTR* and reward sensitivity

Many of the developmental stressors which coincide with changes to neural reward sensitivity are *social* in nature. This is not surprising given that humans have evolved to be highly social. Social perception (Shamay-Tsoory & Abu-Akel, 2016) and behaviors, including mate selection, copulation, and parenting strategies, are at least in part guided by variation in the oxytocinergic system (Carter, 2003; Feldman, Monakhov, Pratt, & Ebstein, 2016). In turn early life social experiences change the oxytocinergic system. Indeed, experiences of childhood abuse coincide with decreased oxytocin availability in the blood and cerebral spinal fluid (Heim et al., 2009; Opacka-Juffry & Mohiyeddini, 2012) and higher DNA methylation of *OXTR* (Gouin et al., 2017). At the neural level, the oxytocinergic system contributes to the response to social behaviors in putatively reward-related regions (Love, 2014) and its interaction with dopamine in these regions influences many important aspects of lifespan development: e.g, mother-infant attachment (Strathearn, 2011), sexual behavior (Melis et al., 2007), and pair bonding (Liu & Wang, 2003). Importantly, the effects of oxytocin on the brain likely depend on expression of its receptor, *OXTR* (Gimpl, Fahrenholz, & Gene, 2001; Yoshida et al., 2009).

If we synthesize the literature on ELS, oxytocin, and reward sensitivity we arrive at a reasonable ACM hypothesis: greater Harshness and Instability in the developmental context could calibrate the oxytocinergic system to promote a reward-sensitive phenotype through its impact on neural reward systems. We know that early life experiences are associated with variation of *OXTR* DNA methylation even in infancy (Krol, Puglia, Morris, Connelly, & Grossmann, 2019) and that variation in *OXTR* DNA methylation is associated with individual differences in the neural response to social cues in both adults (Jack, Connelly, & Morris, 2012; Puglia, Connelly, & Morris, 2018; Puglia, Lillard, Morris, & Connelly, 2015) and infants (Krol et al., 2019). DNA methylation is an epigenetic process by which the addition of a methyl group to *cytosine-phosphate-guanine* (CpG) sites in genes modifies transcription. This modification often reduces transcription, but other types of methylation can increase it (Zhang et al., 2018). A limitation of DNA methylation, however, is that it is often tissue specific (Lokk et al., 2014) and access to human brain tissue is severely limited. Guidance on using epigenetic imaging procedures suggest the importance of animal models in identification of appropriate genes, loci, functional relationship to neural tissue, and appropriate peripheral tissue as reporters of neural tissue (Lancaster, Morris, & Connelly, 2018). Luckily, the prairie vole model system provides us with the translational data necessary to pursue our hypothesis.

2 | Translational epigenetics of early life stress and neural reward sensitivity

A series of studies using the prairie vole by Perkeybile and colleagues (Perkeybile et al., 2019) suggest a functional relationship between developmental experience, *OXTR* DNA methylation in blood and

brain, and *OXTR* mRNA *expression* in the brain. Specifically, the authors found that lower parental care was associated with increased *OXTR* DNA methylation at CpG sites −924 and −934 in the promoter region of *OXTR*. These CpG sites are homologous to sites in humans and are contained within a region of the gene that is important in regulating DNA methylation-dependent transcription of *OXTR* (Kusui et al., 2001). In voles, DNA methylation levels are reduced in both blood and brain tissue (NAcc) with low parental care, indicating the potential for the use of the blood as a marker of early experience. In fact, the authors showed that greater *OXTR DNA* methylation in the blood coincided with decreased mRNA expression in NAcc further validating the potential use of blood as marker of the transcription state of the brain. Interestingly, the environmentally responsive DNA methylation state of the blood was established in early life and persisted into adulthood. This study allows for translation of this model to humans because (a) prairie voles display human-like social behaviors including monogamous pair bonding and both maternal and paternal care of offspring (Gavish, Carter, & Getz, 1981; Getz, Carter, & Gavish, 1981; Tabbaa, Paedae, Liu, & Wang, 2017), (b) CpG sites −924 and −934 are conserved in humans (Perkeybile et al., 2019), giving us suitable loci, and (c) data suggest that DNA methylation in the blood reports on transcription in the NAcc, allowing us to non-invasively assay humans.

2.1 | The current study

Our translational study explores the role of *OXTR* DNA methylation at CpG sites −924 and −934 in the developmental calibration of reward sensitivity. We hypothesize that like in prairie voles, human developmental context calibrates neural reward systems via modification of *OXTR*. Specifically, in line with ACM, greater ELS in the form of harshness and instability should coincide with increased DNA methylation and greater neural reward sensitivity. In turn, increased DNA methylation should also coincide with increased reward sensitivity. Using a longitudinal sample started when participants were 13 years of age, we first modeled developmental context and ELS using multi-reporter data during the first wave of data collection. Separate subsets of these participants later returned as adults (25–27 years of age) to complete the Monetary Incentive Delay (MID) task, an fMRI paradigm, and donated their blood for epigenetic analysis of *OXTR*. We then modeled the relationships between latent factors of developmental context, *OXTR* DNA methylation, and neural reward sensitivity. We predicted that greater Harshness and Instability would be associated with increased reward sensitivity and that this would be mediated or moderated by increased *OXTR* DNA methylation.

3 | METHODS AND MATERIALS

3.1 | Participants

The Virginia Institute of Development in Adulthood (VIDA) sample is comprised of 184 socioeconomically and racially diverse participants followed since they were 13 years of age (now aged ~33). Eighty-nine individuals subsequently underwent functional magnetic resonance imaging (fMRI) as adults (23–27) and 112 participants completed blood draws to assay *OXTR* DNA methylation (29–32). Table 1 displays sample demographics and subsamples included in each of the three study sub-analyses. All portions of this study were approved by the Institutional Review Board. Participants gave informed consent and were compensated for their time. All data were de-identified.

3.2 | Behavioral data procedures

In Wave 1, parents and adolescents (participants) completed several questionnaires. A high proportion of fathers (38%) did not complete data collection. We therefore used data from mothers unless only the father's data were available ($N = 2$). Behavioral measures were chosen based on their relevance to economic and social adversity. Social adversity includes parental experiences which may negatively impact the parent–child relationship (e.g. mental health issues). All measures were previously validated and descriptions as well as who completed them (parent or child) and when (Wave 1 or retrospective) can be found in the Supporting Information. Measures used were: Adverse Childhood Experiences Questionnaire (ACE), Childhood Trauma Questionnaire (CTQ), Childhood Report of Parent Behavior (CRPB), Children's Expectation of Social Behavior (CESB), Neighborhood Quality Questionnaire (NQQ), Beck Depression Inventory (BDI; parent's depression at Wave 1), and household income and education.

3.3 | Exploratory factor analyses

Our factor analysis methods are discussed in detail in the Supporting Information. Behavioral analyses were completed in RStudio (V 1.0.136). We used exploratory factor analysis on 123 individual items from the eight measures. Restricting the covariance matrix reduced these items to 84. Data missingness was at 3.8% and were imputed using multiple imputation estimation of missing data (K-fold = 1,000, missMDA package; Josse & Husson, 2016). An exploratory factor analysis was then conducted on the 84 identified items. Tests of sampling adequacy indicated that the sample was usable (Kaiser–Meyer–Oklin = 0.69; Bartlett's test of sphericity: χ (184) = 19,242.97, $p < .01$, $df = 3{,}486$).

3.4 | Blood collection and DNA extraction

We performed venipuncture between Waves 16 and 17 (28–29 years of age). Eight and a half milliliters of whole blood were collected from each participant using a PAXgene Blood DNA Tube (PreAnalytiX, Hombrechtikon Switzerland). DNA was extracted and *OXTR* DNA methylation was assayed by bisulfite pyrosequencing

TABLE 1 Demographics across study components, parental income and education beginning when participants were 13 years of age"

Demographics breakdown by analysis				
	Exploratory factor analysis	Neuroimaging	Epigenetic	Neuroimaging & epigenetic
Total	184	82	112	59
Gender				
Female	98	44	66	33
Ethnicity				
White/ Caucasian	58%	52%	57%	53%
Black/African American	29%	33%	29%	32%
Other	13%	15%	13%	15%
Parent's highest education				
Below high school	4%	6%	4%	7%
High school or GED	18%	17%	17%	14%
Some college or technical training	27%	29%	28%	29%
Associate's degree	6%	4%	5%	3%
Bachelor's degree	15%	11%	13%	8%
Some graduate work	7%	10%	9%	10%
Post college degree	19%	20%	18%	25%
Annual household income				
under $5,000	3%	4%	2%	2%
$5,000–$9,999	4%	4%	5%	5%
$10,000–$14,999	5%	5%	4%	5%
$15,000–$19,999	5%	5%	6%	5%
$20,000–$29,999	17%	18%	19%	22%
$30,000–$39, 999	8%	7%	9%	7%
$40,000–$59,999	20%	23%	19%	22%
$60,000 or more	30%	27%	29%	27%

Note: Exploratory factor analysis was completed using the entire sample. Highest education reflects mother's highest education achieved during Wave 1 of data collection except for when mother's was not available in which case we used the father's data ($N = 2$).

using previously established methods(Jack et al., 2012; Puglia et al., 2015, 2018; see Supporting Information). Samples were run in triplicate, with methylation score averages used for all further analyses (average deviation of 1.86%). Methylation percentages for the two CpG sites were correlated at $r = .65$.

3.5 | fMRI data acquisition and preprocessing

Participants completed the MID Task to assay BOLD response related to the anticipation of monetary rewards. The paradigm is well described in the literature (Knutson, Westdorp, Kaiser, & Hommer, 2000) and in the Supporting Information. Briefly here, MID requires participants to press a button following a reward or punishment cue in order to earn money or prevent monetary loss. Participants briefly see a fixation cross in between pressing their button and receiving feedback and this allows us to look at the anticipation of monetary rewards.

Data were acquired using a Siemens 3.0 Tesla MAGNETOM Trio high-speed MRI device. Stimuli were presented through a CP transmit/receive head coil with an integrated mirror. Structural T1 echo-planar images (EPI) were first obtained (176, 1-mm slices). Functional T2-weighted EPIs were collected during MID (224 per MID run, volume = 28, 3.5-mm slices). Imaging data were preprocessed and analyzed using FMRIB Software Library (FSL) software (version 5.98; www.fmrib.ox.ac.uk/fsl). Standard pre-processing steps were completed before using FSL's fMRI Expert Analysis Tool (FEAT) to model anticipation to monetary gain and loss using the standard lower-level contrasts(Knutson et al., 2000; Supporting Information).

3.6 | fMRI data analysis

Associations between developmental context and *OXTR* DNA methylation on task-specific activity were assessed using FLAME. We corrected for multiple comparisons using estimated smoothness and Gaussian Random Field Theory to determine cluster size ($Z = 2.3$, $p = .05$). We conducted both region of interest analyses for a priori

brain regions (NAcc, caudate, and OFC) and exploratory whole-brain analyses. Binarized region of interest (ROI) masks were created based on the Harvard-Oxford Subcortical Atlas probability map.

3.6.1 | Developmental context and adult reward anticipation

Each latent variable factor identified in the behavioral analysis (see Behavioral Section 3) was centered to the subsample ($N = 82$) and entered together into one general linear model. Negative and positive contrasts were computed to determine correlations between each latent construct and neural response to reward anticipation while statistically adjusting for the other constructs.

3.6.2 | Interaction between *OXTR* DNA methylation and developmental context on reward anticipation

Each latent factor and methylation percentage was Z-transformed on the overlapping sample ($N = 59$) and interaction terms computed. In accordance with best practices, mean anticipation reward, a developmental factor, DNA methylation at one CpG site, and the interaction term were entered into the model, but only the interaction was estimated. All models with DNA methylation as a predictor also included self-reported sex as a nuisance variable. Others have found sex-based methylation differences (Puglia et al., 2015), however we did not (see Section 3).

We conducted simple slopes analyses on linear regression models (Preacher, Curran, & Bauer, 2006) to understand interaction effects. We extracted the mean *Z*-statistic for the Reward Anticipation > Neutral contrast for each ROI from a model without covariates. Multiple linear models were used to probe the interaction effects between a single latent factor and a single CpG site on mean activation at each ROI. All models were adjusted for self-reported sex. Models were assessed for normality of residuals, linearity, heteroscedasticity, and influence.

4 | RESULTS

4.1 | Three factor solution for developmental context analysis

Instead of a Harshness and an Instability latent construct, a three-factor solution emerged. Factors were extracted based on the following rules: (a) factors had to have an Eigenvalue greater than one and (b) each factor had to substantially increase the variance explained. A three-factor solution explained 28% of the data, and subsequent factors did not significantly increase this. The solution was examined using the ordinary least square minimum residuals measure bootstrapped with 1,000 iterations. Model fit was good (RMSEA = 0.02, 90% confidence interval = 0.02 to 0.148, Bayesian information criterion = −1075.92) though Chi Square testing rejected that three factors were sufficient ($\chi^2 = 15{,}804.82$, $p < 0$). Nevertheless, three factors struck the balance between simplicity and completeness. Factors were characterized as Neighborhood Harshness, Family Harshness, and Abuse & Disorder (see Figure 1; Supporting Information; Table 2 for item breakdowns). Factor scores were extracted using the ten Berge algorithm to preserve the correlations between factors (ten Berge, Krijnen, Wansbeek, & Shapiro, 1999).

4.2 | Greater Neighborhood Harshness coincides with increased neural reward sensitivity in a priori ROIs

Neighborhood Harshness was associated with increased activation in NAcc, caudate, and OFC in response to reward anticipation while controlling for Family Harshness and Abuse and Disorder. Associations between Family Harshness or Abuse and Disorder and reward anticipation at these ROIs were not significant when controlling for the other two factors.

4.3 | *OXTR* DNA methylation does not mediate the association between Neighborhood Harshness and neural reward sensitivity

Step two of creating a mediation model involved investigating the simple associations between Neighborhood Harshness and *OXTR* DNA methylation. We first determined that DNA methylation did not vary by race (−924: $F(1,110) = 0.54$, $p = .46$; −934: $F(1,110) = 1.5$, $p = .22$) or self-reported sex (−924: $F(1,110) = 0.13$, $p = .72$; −934: $F(1,110) = 0.0$, $p = .98$) in our current sample. We next created a general linear model predicting DNA methylation from Neighborhood Harshness, but this was found to be non-significant (−924: $F(3{:}108) = 0.34$, $p = .79$; −934: $N = 112$, $F(3{:}108) = 0.57$, $p = .63$. Without this direct relationship, we could not further pursue a mediation model.

4.4 | *OXTR* DNA methylation blunts the association between Neighborhood Harshness and neural reward sensitivity

There was a two-way interaction in caudate, and OFC between Neighborhood Harshness and methylation at CpG site −924 (Table 3; Figure 2a). Interactions between Neighborhood Harshness and CpG site −934 reached significance in caudate (Table 3; Figure 2b) and trended in NAcc, but not OFC. Simple slopes analysis (Figure 3) indicated that *OXTR* methylation appears to blunt the effect of adolescent Neighborhood Harshness in caudate. However, higher methylation at CpG −924 was associated with increased OFC activation to reward anticipation, but only with low Neighborhood Harshness (Figure 4).

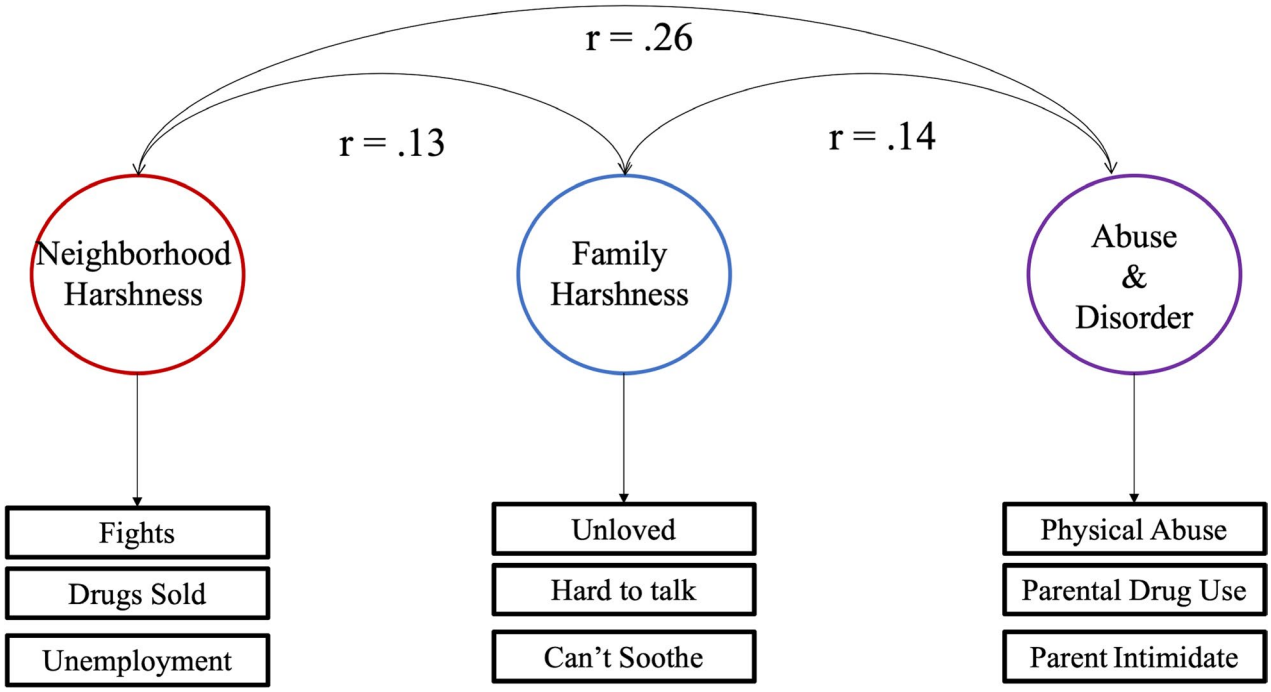

FIGURE 1 Three-factors that represent developmental context: Neighborhood Harshness, Family Harshness, Abuse and Neglect. Curved arrows indicate correlations between factors and the correlation coefficients are shown below each line. The boxes under each latent factor indicate a short description of the three most strongly loaded items for that factor

TABLE 2 Local maxima for Reward > Neutral × Developmental Context Analyses. Tables shows clusters significantly related to Neighborhood Harshness. For whole-brain analyses, brain regions are approximate and based on Harvard-Oxford Cortical and Subcortical Atlases

	Local maxima					
	Max *Z* Stat	*X*	*Y*	*Z*	*k*	*p*
ROI analysis: Nucleus accumbens						
Right	3.82	14	22	−2	140	.00677
Left	3.14	−10	20	2	55	.0466
ROI analysis: Caudate						
Right	3.82	14	22	−2	357	.000699
Left	3.3	12	−4	18	155	.0197
Whole-brain analysis						
Brain region						
Right caudate	3.82	14	22	−2	1,021	1.24E−05
Right parietal operculum	3.66	30	−28	24	656	.000702
Left occipital pole	3.84	−22	−104	2	493	.0054
Left temporal gyrus	4.24	−48	−44	−6	450	.00956
Right occipital pole	3.72	24	−92	10	377	.0263

We did not find interaction effects between *OXTR* DNA methylation and either the Family Harshness or Abuse and Disorder constructs on neural activation at our a priori ROIs. However, whole-brain exploratory analysis across all three developmental factor-types revealed interaction effects with both CpG sites in regions of the default mode network (Supporting Information Figures S5 and S7).

TABLE 3 Results of regions of interest analyses modeling Reward > Neutral × Neighborhood Harshness × *OXTR* methylation. Local maxima reflect voxels in a priori regions maximally associated with the interaction of Neighborhood Harshness and methylation at either CpG site −924 or −934

	Local maxima					
	Max *Z* Stat	*X*	*Y*	*Z*	*k*	*p*
CpG 924						
Caudate						
Right	3.64	12	16	8	137	.0247
Left	3.3	−14	18	−2	119	.0362
Orbital frontal cortex						
Left	3.08	−48	22	−2	155	.0357
CpG 934						
Caudate						
Right	3.7	16	16	6	274	.00191

5 | DISCUSSION

Our study tested a translational model derived from the prairie vole model system which links ELS and *OXTR* DNA methylation to adult neural reward systems. Based on ACM, we expected to model developmental context as Harshness and Instability, to associate higher levels of these dimension to increased *OXTR* DNA methylation, and to associate DNA methylation with increased neural activation in putatively reward-related regions of interest. We found partial support for our original hypotheses. Findings suggest that (a) our developmental context was best modeled by proximal and distal measures of ELS, (b) reward and motivational neural systems calibrated more to neighborhood harshness rather than immediate family dynamics, (c) greater neighborhood harshness coincided with a more reward-sensitive endophenotype and (d) greater *OXTR* DNA methylation in the promoter region was associated with the diminished importance of adolescent neighborhood harshness in the calibration of putative neural reward regions.

5.1 | Neighborhood characteristics as the calibrating developmental environment

We first established a three latent factor model of adolescent developmental context. These factors—Neighborhood Harshness, Family Harshness, and Abuse and Disorder—included different types and intensities of Harshness, but not Instability. Though research on ELS and psychobiology has grown remarkably, we have little understanding of how different types of adversity may differentially impact the calibration of stress systems (Chen & Paterson, 2006; McLaughlin et al., 2014). We found that the distal Neighborhood Harshness construct, and not the proximal Family Harshness, and Abuse and Disorder constructs, was related to neural response to reward anticipation. Above individual SES, neighborhood SES and neighborhood dynamics influence risk-taking (Furr-Holden, Milam, Reynolds, MacPherson, & Lejuez, 2012). Mortality cues in neighborhoods have been related to life history behaviors such as early sexual debut (Carlson, McNulty, Bellair, & Watts, 2014; Wilson & Daly, 1997). Notably, a recent study found that neighborhood poverty, above individual SES, was associated with decreased activation in striatum during a *response inhibition* task in children and adolescents (Tomlinson et al., 2020). Adding to these previous findings, our data suggest that neighborhood factors, above individual family

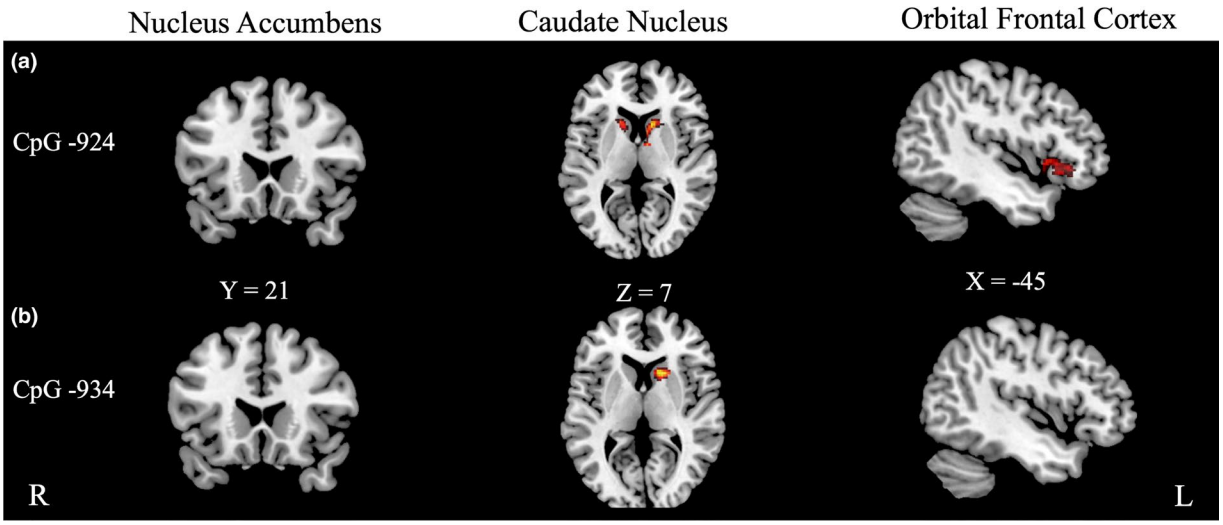

FIGURE 2 Significant results for regions of interest analyses modeling Reward > Neutral × Neighborhood Quality × *OXTR* methylation. (a) Methylation at *OXTR* CpG site −924 moderated the relationships between Neighborhood Harshness and Adult Reward Sensitivity in caudate and left orbital frontal cortex, but not nucleus accumbens. (b) Methylation *OXTR* CpG site −934 moderated the relationship between Neighborhood Harshness and Adult Reward Sensitivity in left caudate, but neither nucleus accumbens nor orbital frontal cortex

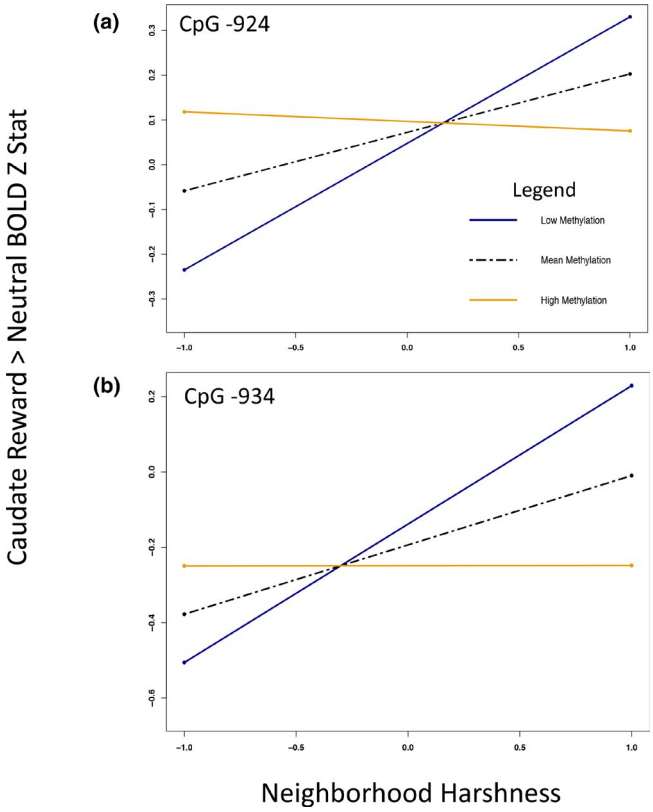

FIGURE 3 *OXTR* DNA methylation blunts association between Neighborhood Harshness and reward sensitivity in Caudate. Maximum likelihood estimation of simple slopes for *OXTR* × Neighborhood Harshness interactions on neural activation in caudate for both CpG sites. (a) High methylation (orange line), defined as one standard deviation away from the Z-transformed methylation percentage, blunts the positive association between Neighborhood Harshness and reward activation relative to individuals with mean (black dashed line) or low levels of methylation (1 standard deviation below the mean, blue line). (b) The same association is found in CpG site −934

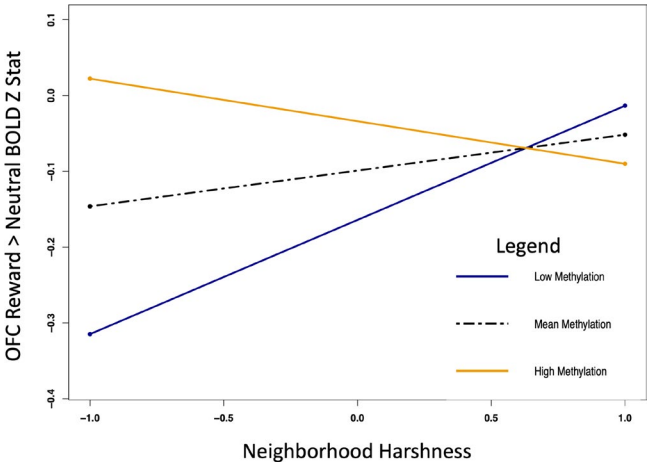

FIGURE 4 OXTR DNA Methylation reverses association between Neighborhood Harshness and reward sensitivity in OFC. Maximum likelihood estimation of simple slopes for *OXTR* × Neighborhood Harshness interactions on neural activation in OFC. Individuals with High Methylation at CpG site −924 (orange line) show increased anticipatory activation in OFC if they experienced low Neighborhood Harshness during adolescence. In contrast, those with low levels of methylation (blue line) show low activation in the OFC if they experienced low Neighborhood Harshness, but higher activation if they experienced high Neighborhood Harshness. This indicates an epigenetic by environment interaction on OFC response to the anticipation of rewards

factors, calibrate neural reward systems towards a more appetitive endophenotype.

5.2 | An epigenetically derived differential susceptibility model

Greater DNA methylation in CpG sites −924 and −934 blunted the association between Neighborhood Harshness and reward-related activation in caudate. Those with low methylation had strong associations between Neighborhood Harshness and reward sensitivity in the expected life history directions (greater reward sensitivity). However, those with high methylation had no association at all. In other words, our effect looked like an epigenetically derived differential susceptibility model (Belsky & Pluess, 2009), where low methylation instead of a particular genotype rendered participants susceptible to the adolescent context. Importantly, this model would not extend to OFC findings, where we saw a full cross-over effect, perhaps owing to its regulatory rather than appetitive role in reward and motivational processes (Haber & Knutson, 2009). Future animal studies are particularly poised to disentangle differential effects across neural regions.

Another way to look at the data is to suppose that earlier experiences led to DNA methylation and this in turn led to decreases in adolescent neural plasticity to the immediate context. This sequence would align well with ACM's position that more extreme stressors during earlier and more sensitive periods will lead to physiological systems (in this case, regions of the brain) being less open to iterative input from the environment. In the face of high mortality cues, the need for experiential canalization increases. In such a case, ACM predicts that we would trade plasticity and flexibility in favor of fixed action patterns useful for survival (Ellis, Giudice, et al., 2017; Figueredo et al., 2006). Epigenetic tuning at early stages of development (Krol et al., 2019) and even in utero (Unternaehrer et al., 2016) may then better explain the diminished receptivity to environmental inputs in adolescence.

5.2.1 | Risk or resilience?

Given the association between ELS and dysregulated motivational systems to poorer mental health outcomes, it is natural to wonder which differential susceptibility pattern might constitute risk or resilience. From an allostatic load perspective, short-term gains could lead to long-term risk factors (McEwen & Gianaros, 2011). The ACM

perspective, goes further to say that the ability of any physiological calibration to act as a risk or resilience factor is dependent on the match between the phenotype and the environment (Ellis, Bianchi, Bianchi, Griskevicius, & Frankenhuis, 2017). Like in other differential susceptibility models, any mechanistic effects are contextually bound. In other words, there is nothing inherently pathophysiological about having more or less neural plasticity, methylation, or neural reward sensitivity.

However, there are still clinical implications. If the model is true, adolescents with low *OXTR* methylation will have neural reward systems susceptible to *the influence of their environments*. Accordingly, interventions will be maximally effective for individuals with emerging mental health issues related to reward endophenotypes. It *also* means that highly methylated and mentally healthy adolescents may be resilient to aspects of the adolescent context that might otherwise compromise their more susceptible peers. Effects are contextually bound. These are conjectures, but they do imagine exciting new opportunities from which to maximize clinical outcomes based on molecular profiles, as others have called for (Bakermans-Kranenburg & van Ijzedoorn, 2014).

5.2.2 | Limitations and future directions

While results of these analyses are bolstered by the mechanistic and functional animal data, our conclusions are still preliminary and necessitate replication and expansion through future studies. A clear limitation of our study is the limited number of people with complete developmental, neuroimaging, and epigenetic data ($N = 59$). Recent multisite longitudinal data collection efforts may shed light on some of the developmental sequalae suggested here (Casey et al., 2018), but targeted data collection is also warranted. Future data collection should focus on translating animal models as these provide the best mechanistic support. Importantly, our analysis failed to show a significant association between *OXTR* DNA methylation and any of our latent factors of developmental context despite others having found increased DNA methylation with experiences of childhood abuse (Smearman et al., 2016). Because DNA methylation occurs in utero and can change with very early life experience (Krol et al., 2019; Perkeybile et al., 2018; Unternaehrer et al., 2016), obtaining measures of DNA methylation at birth and through development along with developmental context may be necessary. Elucidating how different aspects of the developmental environment tune oxytocinergic and motivational systems can bring us closer to mechanisms of normative development and contextually bound understandings on putative endophenotypes of psychopathology.

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CONFLICT OF INTEREST

The authors, Marlen Z. Gonzalez, Kelly L. Wroblewski, James A. Coan, Joseph P. Allen, and Jessica J. Connelly, declare no biomedical financial interests or potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data used to generate these analyses are available from the authors upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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