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The differential impact of oxytocin receptor gene in violence-exposed boys and girls

Livia C. Merrill[a,*], Christopher W. Jones[a], Stacy S. Drury[a], Katherine P. Theall[b]

[a] Tulane University School of Medicine, 1430 Tulane Ave., New Orleans, LA 70112, United States
[b] Tulane University School of Public Health and Tropical Medicine, 1440 Canal St., New Orleans, LA 70112, United States

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ABSTRACT

Childhood violence exposure is a prevalent public health problem. Understanding the lasting impact of violence requires an enhanced appreciation for the complex effects of violence across behavioral, physiologic, and molecular outcomes. This subject matched, cross-sectional study of 80 children explored the impact of violence exposure across behavioral, physiologic, and cellular outcomes. Externalizing behavior, diurnal cortisol rhythm, and telomere length (TL) were examined in a community recruited cohort of Black youth. Given evidence that genetic variation contributes to individual differences in response to the environment, we further tested whether a polymorphism in the oxytocin receptor gene (*OXTR* rs53576) moderated associations between violence and youth outcomes. Exposure to violence was directly associated with increased externalizing behavior, but no direct association of violence was found with cortisol or TL. Oxytocin genotype, however, moderated the association between violence and both cortisol and TL, suggesting that pathways linked to oxytocin may contribute to individual differences in the physiologic and molecular consequences of violence exposure. Sex differences with OXTR in cortisol and TL outcomes were also detected. Taken together, these findings suggest that there are complex pathways through which violence exposure impacts children, and that these pathways differ by both genetic variation and the sex of the child.

1. Introduction

Violence exposure, both in the home and in the community, is a public health problem with implications for youth (Richters, 2017; Cooley-Quille, 2001; Finkelhor et al., 2015). Although linked to overlapping negative consequences that are often co-occurring, the impact of violence exposure, at both the community and household level, across multiple outcomes has seldom been examined concurrently in youth (Theall et al., 2017). Despite evidence that gene by environment interactions influence a range of different outcomes in relation to violence, few studies have explored how genotype moderates the impact of violence in youth (Martinez-Torteya, 2009; Caspi, 2002). Given the unfortunate prevalence of violence coupled with the established links between violence and adverse behavioral, physiologic, molecular, and health outcomes, defining how violence exposure interacts with genetic factors to influence both vulnerability and resilience in children is paramount (Moylan, 2010; Suglia, 2010; Shalev et al., 2013; Fowler, 2009).

One established consequence of violence exposure is externalizing behavior, including impulsivity, aggression, and oppositional behavior (Moylan, 2010; Appleyard, 2005). Externalizing behavior in childhood is associated with higher rates of later delinquency, perpetration of violent acts, imprisonment, and maladjustment (Farrington, 1991; Campbell, 2000; Wakefield and Wildeman, 2011). Typically, externalizing behaviors increase over childhood, with males demonstrating more externalizing behavior than females later in development (Miner and Clarke-Stewart, 2008; Deater-Deckard, 1998). Multiple studies have linked violence and externalizing behavior. Children and adolescents exposed to domestic violence and physical abuse exhibit higher rates of externalizing behavior, premeditated aggression, fighting, and trouble in schools (Moylan, 2010; Deater-Deckard, 1998; Aisenberg and Herrenkohl, 2008), which subsequently is associated with adult criminal violence and higher suicide rates (Farrington, 1991; Swogger and et al, 2015; Coêlho et al., 2016). This link between violence and aggression appears to be stronger in boys, although this may reflect increased exposure to violence in boys (Deater-Deckard and Dodge, 1997; Brookmeyer et al., 2005; Ozer and Weinstein, 2004; Selner-O'Hagan, 1998; Martel, 2013).

Violence exposure also impacts physiologic pathways, including the Hypothalamic-Pituitary Adrenal (HPA) axis, a primary stress-response

* Corresponding author at: Tulane University School of Medicine, 1430 Tulane Ave. 2720, New Orleans, LA 70112, United States.
E-mail addresses: lmerril@tulane.edu (L.C. Merrill), cjones35@tulane.edu (C.W. Jones), sdrury@tulane.edu (S.S. Drury), ktheall@tulane.edu (K.P. Theall).

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system with cortisol as the downstream effector. Cortisol's diurnal rhythm is characterized by a peak after waking (cortisol awakening response; CAR) and a steady decline across the day (Price et al, 1983). Typically, female adolescents have higher basal cortisol levels than males (Klimes-Dougan, 2001). Children exposed to past and recent trauma exhibit blunted morning cortisol levels and elevated evening cortisol levels (Bevans et al., 2008). Children exposed to community violence also have lower morning cortisol levels and a flatter diurnal rhythm (Suglia, 2010). However, violent crime environments have also been associated with a steeper diurnal cortisol rhythm (Theall et al., 2017). Similar to the patterns with externalizing behavior, sex differences exist, with exposed boys exhibiting flatter diurnal slopes than exposed girls (DeSantis, 2007; Elzinga, 2008).

The effects of community and domestic violence exposure are not only present in behavioral and physiologic systems, but also cellular stress, indexed by telomere length (TL) (Shalev, 2012; Drury et al., 2014). Telomeres are repetitive DNA sequences that cap chromosomes to provide protection from DNA damage or inappropriate fusion. Telomeres shorten with each cellular division, and when they reach a critical length, can trigger cellular senescence or apoptosis (de Lange, 2002; Campisi and di Fagagna, 2007). TL, which is influenced by oxidative stress, cellular metabolism, and DNA damage, also contributes to global epigenetic regulation, particularly in the *peri*-telomeric regions (von Zglinicki, 2002; Ye et al., 2014). Females appear to have longer TL across the life span; however, debate exists (Drury et al., 2015; Zhu et al., 2011; Benetos et al., 2001; Aubert et al., 2012). Youth exposed to current and early life violence in the home and community have been reported to have both shorter TL and greater TL attrition across childhood (Theall et al., 2017; Shalev et al., 2013; Tyrka et al., 2010 Shalev et al., 2013; Tyrka et al., 2010). Violence within the household has also been associated with shortened TL that is more pronounced in girls (Drury et al., 2014).

While there is evidence that violence exposure has adverse effects across behavioral, physiologic, and molecular systems, children are not uniformly impacted. Evidence suggests that individual differences and social support contribute to variable outcomes in violence-exposed children (Brüne, 2012; Mahon et al., 2013; Hammack et al., 2004). Genetic differences in neural systems related to social support provide a unique opportunity to examine the cross-domain impact of violence on youth. Oxytocin is a neuropeptide linked to human social behavior and social support (Bartz, 2011; Heinrichs, 2003; Heinrichs, 2009; Fand et al., 2014). One single nucleotide polymorphism (SNP) in the oxytocin receptor gene (OXTR, rs53576) has been studied in conjunction with a range of adversities and has been associated with social behavior, cortisol reactivity, and TL (Bakermans-Kranenburg and van IJzendoorn, 2014; Smearman et al., 2016; Auer et al., 2015). OXTR genotype interacted with family environment to predict coping and positive affect after childhood maltreatment, as well as influence the perception of social support in adolescents (Lucht et al., 2009; Hostinar et al, 2014). In healthy adults, OXTR genotype interacted with perceived social support to predict utilization of support during acute stress, subsequently reducing cortisol levels (Chen et al., 2011; Kim, 2010). OXTR genotype also moderated the relationship between parental support and TL in Black youth (Smearman et al., 2016). Together, these findings support the hypothesis that OXTR genotype may moderate the link between violence exposure and behavior, physiologic, and molecular outcomes.

Leveraging a unique high risk Black cohort of children matched for exposure to potential confounders, we explored how violence exposure, defined as direct violence toward the child or the witnessing of violence inflicted on a loved one, was associated with externalizing behavior, diurnal cortisol patterns, and TL, measured concurrently in the same individual. We also tested whether OXTR genotype moderated the relationship between violence and these outcomes. To our knowledge, this is the first study to assess the impact of violence exposure, and genetic moderators of this exposure, concurrently across behavioral, physiologic, and cellular outcomes. The evidence of sex differences across all outcomes prompted us to directly test for sex differences.

2. Materials and methods

2.1. Sample

Children aged 5–15 years were recruited from the greater New Orleans, LA area between January 2012 and July 2013 to participate in a cross-sectional study examining the association of neighborhood and family conditions on child health. Families were recruited through schools and street outreach techniques, including ethnographic mapping and targeted sampling (Watters and Biernacki, 1989). Recruitment neighborhoods were identified using the community identification process, a mapping method to record epidemiological indicators of the prevalence and incidence of community violence and other selected social and health conditions (Tashima, 1996). Interested families contacted the research site to schedule an appointment. Maternal caregivers provided information about multiple levels of the child's social ecology (i.e. household and neighborhood) and physical traits (i.e. age) using an interview-assisted computer survey administered face-to-face at the research site (Questionnaire Development System, QDS, Nova Research, Bethesda, MD). Trained interviewers recorded oral responses and measurements (i.e. BMI) on the computer. Written informed consent was obtained from caregivers. Our analysis was *a priori* limited to only Black youth to minimize the potential for confounding by racial identity.

2.2. Subject matching

Propensity scores for violence exposure were calculated by computing the predicted probability of secondary violence exposure, based on potential confounders such as household socioeconomic status (maternal education and income), marital status, household chaos through Confusion, Hubbub, and Order Scale (CHAOS), maternal and child age, sex, and maternal adverse childhood life experiences (ACE) (Oakes and Johnson, 2006). Children were matched 3:1 (with replacement), based on age within a year, exposure to Hurricane Katrina (Disaster Experience Questionnaire; DEQ), and propensity score within 0.05 caliper of living in a high violence neighborhood (i.e., those with a propensity score of 0.20 were matched to children with scores between 0.15 and 0.25).

2.3. Violence exposure

The primary exposure of interest, witnessing violence, whether direct or indirect, in the community or home, was measured by an adaptation from the minor and major life events from the Preschool Age Psychiatric Assessment (PAPA) (Egger, 2006). Caregivers were asked survey questions to assess exposure to violence, if the child had been in a situation where he/she could have been hurt or mistreated, or witnessed a loved one get hurt or mistreated, examined as a dichotomous variable; exposed to violence (either) or not.

2.4. DNA extraction

DNA for both genotyping and telomere length (TL) was extracted from Isohelix SK1 buccal swabs (Cell Projects, Kent, United Kingdom) by using QIAamp DNA mini kit protocol (Qiagen, Valencia, CA). DNA purity was determined by using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA). DNA concentration was quantified by Qubit dsDNA BR assay kit (Invitrogen, Carlsbad, CA), and its integrity was confirmed by agarose gel electrophoresis to ensure high molecular weight DNA. Samples were stored at −80 °C. After extraction, samples underwent only one freeze-thaw cycle to minimize DNA degradation.

2.5. Oxytocin receptor (OXTR) genotyping

OXTR (rs53576) allele status was determined using TaqMan SNP assay, Applied Biosystems (C_3290335_10). All samples were run in duplicate, with known controls. Samples with inconsistent duplicates were repeated. Genotyping was done blind to other outcomes

2.6. Externalizing behavior

Caregivers completed the Child Behavior Checklist (CBCL), which assesses emotional and behavioral problems (Achenbach, 1991). This well-validated questionnaire identifies symptoms of internalizing and externalizing behaviors. The normalized T-score for externalizing behavior was utilized in analyses.

2.7. Cortisol

Each child provided eight diurnal saliva samples across two separate days: upon awakening, 30 min after waking to capture the cortisol awakening response (CAR), early afternoon, and prior to sleep. Saliva was obtained by passive drool and stored in freezers. These saliva samples were quantitatively analyzed for cortisol concentration with a commercially-available validated competitive enzyme-linked immunosorbent assay (www.salimetrics.com). All samples were run in duplicate. Any samples that resulted in a CV greater than 7% were repeated on a subsequent plate. If the concentration of cortisol in the sample was above the measurement threshold, the sample was diluted at a 1:10 ratio with assay diluent and repeated. Values (ug/dL) were log-transformed for subsequent analyses.

2.8. Buccal telomere length (bTL)

bTL, as represented by the T/S ratio, was determined by monochrome multiplex quantitative real-time polymerase chain reaction (MMqPCR) from DNA extracted from buccal (cheek) swabs as in previous studies (Drury et al., 2014). All samples were performed in triplicate and duplicated on a second plate. Samples with high CV (10% intra-and 6% interassay CV) were removed from analysis or repeated. bTL ratio was determined by the average of the triplicates from both plates. Children without bTL data did not significantly differ ($P > 0.05$) from children with bTL data on study measures.

2.9. Analytical approach

Univariate, bivariate, and multivariate analyses were performed using SAS version 9.4 (Cary, NC). Hardy-Weinberg equilibrium was used to assess genotype frequencies. Bivariate analyses examined potential confounders between exposure to violence and externalizing behavior, cortisol, and bTL, through Pearson's or Spearman's rank-order correlation coefficients. Key covariates or potential confounders, other than those part of the match, included socio-demographics: child sex, age or pubertal stage, body mass index (BMI), and maternal education. Puberty status was categorized by maternal-reported Pubertal Development Scale (Petersen, 1988) converted to Tanner stage, child sex, and age (Shirtcliff, 2009).

Significantly associated covariates with both cumulative exposure to violence and externalizing behavior, cortisol, or bTL that changed the estimate between violence exposure and the dependent outcome by more than 10%, as well as those considered theoretically important, were included in the multivariate models. Multivariate models were run independently for the three dependent outcomes of interest, i.e. externalizing behavior, cortisol, or bTL. For externalizing behavior (continuous) and bTL (continuous), multivariate analysis included linear regression, and an interaction between violence exposure and OXTR allele status, as well as an interaction between violence exposure, OXTR allele status, and child sex. Thirty-eight percent of enrolled families had more than one child participate (range 1–5); therefore, to account for correlation between siblings or children living in the same household and to ensure correlated data did not inflate findings, generalized estimating equations (GEE) analyses were employed using an unstructured correlation structure. Furthermore, analyses within the main effects and interaction models of both externalizing behavior and bTL stratified by child sex were conducted.

Mixed-effects multivariate models, using PROC MIXED, were employed for repeated measures of cortisol over time to account for within-subject correlation, expressed by the intraclass correlation coefficient (ICC). To capture the diurnal rhythm of cortisol across the day, two dummy coded variables, the cortisol awakening response (CAR) and time since waking (TSW, in hours), were added to the model to assess the diurnal slope of cortisol. A three-way interaction of violence exposure, OXTR allele status, and TSW were included in the model to determine the dynamics of diurnal cortisol and to allow for deconstruction of variance via the included two-way interactions for determination of their influence on cortisol across the day. Also, the mixed-effects multivariate model included random effects of intercept and TSW. Empirically relevant covariates included in the MIXED model were pubertal stage, maternal education level, and BMI. Pubertal stage was included instead of child age due to their collinearity and the greater direct effect of pubertal stage on diurnal cortisol. As with externalizing behavior and bTL, analyses were also conducted stratifying by sex. Due to modeling of cortisol requiring time since waking, we were not powered to test the interaction with violence exposure, genotype, and sex, but rather ran the interactions within each sex.

Due to missing information from maternal report or biological samples, sample size for analyses varied slightly for externalizing behavior (N = 69), diurnal cortisol (N = 61), and bTL (N = 76).

3. Results

Characteristics of the cohort are presented in Table 1. The cohort was 54% female and children were on average 10.26 years of age. Thirty percent of children were reported to have directly witnessed violence to themselves or to someone close to them. Sixty-nine percent of children possessed the GG genotype. Given the low prevalence of homozygous AA (2%) individuals, analyses were completed where A allele carriers were collapsed into one group containing AA and AG genotypes (31%). Genotypes did not deviate from Hardy-Weinberg

Table 1
Demographics of Sample.

	N (%) or mean (SD)	OXTR GG	OXTR AA/AG
Sex of child			
Male	37 (46.3%)	26 (32.5%)	11 (13.8%)
Female	43 (53.8%)	29 (36.3%)	14 (17.5%)
Child age	10.26 (2.92)	10.16 (2.79)	10.48 (2.97)
Mother's education			
< High school	22 (27.5%)	15 (18.8%)	7 (8.8%)
High school degree or GED	20 (25%)	15 (18.8%)	5 (6.3%)
Some college or more	38 (47.5%)	25 (31.3%)	13 (16.3%)
BMI	19.97 (5.70)	19.62 (5.61)	20.73 (5.94)
Telomere length*,[1]	1.69 (0.05)	1.70 (0.05)	1.68 (0.03)
Externalizing behavior	51.15 (13.24)	52.40 (14.24)	48.27 (10.34)
Witness violence			
Yes	23 (29.5%)	13 (28.9%)	10 (27.0%)
No	55 (70.5%)	31 (68.95%)	26 (70.3%)
OXTR			
GG	55 (68.8%)		
AA/AG	25 (31.3%)		
Puberty Stage [0–4]	2.30 (1.30)	2.27 (1.34)	2.36 (1.22)

[1] Average buccal cell telomere length as represented by the telomere repeat copy number to single gene (albumin) copy number (T/S) ratio.
* P-value < 0.05.

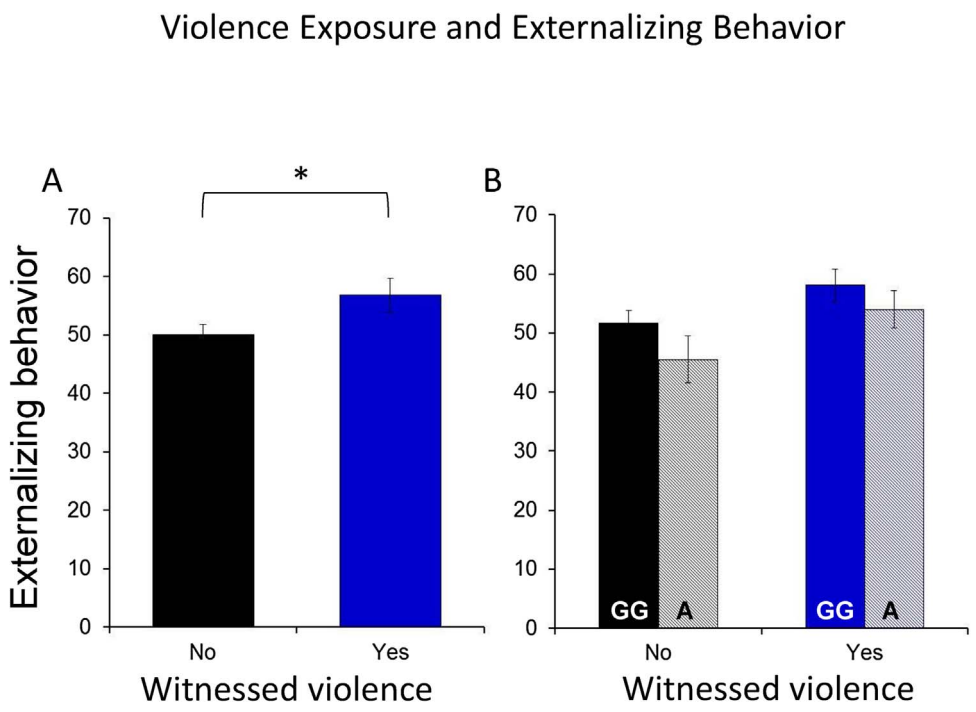

Fig. 1. The impact of violence exposure on externalizing behavior (N = 69). Violence exposure was significantly associated with externalizing behavior *(A)*, but was not moderated by OXTR genotype. *(B).*p > 0.05*

equilibrium (Fig. 1).

Child BMI was not correlated with bTL, and controlling for BMI did not affect results. Age of child was not significantly correlated with violence exposure. Genotype, violence exposure, and age were not significantly different by sex of child.

3.1. Externalizing behavior

A base model not accounting for genotype but controlling for other covariates revealed that children exposed to violence exhibited increased externalizing behavior ($\beta = 5.786$, $P = 0.007$).

Multivariate results outlining the effect of violence exposure and OXTR allele status on externalizing behavior are presented in Table S1. Witnessing violence was significantly and positively associated with increased externalizing behavior (Table S1; Model 1; $\beta = 5.429$; $P = 0.050$). There was no direct effect of OXTR and no interaction between violence and OXTR on externalizing behavior (Table S1; Model 2). Analyses revealed that there was no interaction between violence exposure, OXTR, and sex (Table S1; Model 3).

3.2. Diurnal cortisol

A base model not accounting for genotype but controlling for other covariates revealed that children exposed to violence did not exhibit altered diurnal cortisol rhythm ($\beta = -0.011$, $p = 0.942$).

Multivariate results outlining the effect of violence exposure and OXTR allele status on diurnal cortisol are presented in Table S2. A main effects model (Table S2; Model 1) captured waking basal cortisol levels ($\beta = 3.20$; $P < 0.0001$), a cortisol awakening response (CAR; $\beta = 0.735$; $P < 0.0001$), a decline in cortisol across the day ($\beta = -0.110$; $p = 0.0002$) and possessed a nonlinear trend across the day (Fig. 2; $\beta = 0.01$; $P = 0.028$). There was not a direct effect of witnessing violence or OXTR genotype on diurnal cortisol, but, given our *a priori* hypothesis, we tested whether genotype interacted with violence to influence cortisol patterns. A three-way interaction between witnessing violence, OXTR allele status, and TSW predicted cortisol across the day at trend level (Table S2; Model 2; $\beta = -0.080$; $P = 0.079$; Fig. 2). Stratified analyses by child sex revealed that violence exposure and OXTR allele status impacted diurnal cortisol rhythm in boys only (Table S2; Model 3; $\beta = -0.192$; $P < 0.0001$). GG boys exhibited a steeper diurnal cortisol rhythm when exposed to violence, but a flatter rhythm in a non-exposed environment. Females did not show a relationship between cortisol, OXTR, and violence.

3.3. Buccal telomere length (bTL)

A base model not accounting for genotype but controlling for other covariates revealed a trend level effect of children exposed to violence having shorter bTL ($\beta = -0.018$, $p = 0.071$).

Multivariate results outlining the effect of violence exposure and OXTR allele status on bTL are presented in Table S3. Genotype and violence were not independently associated with bTL (Table S3; Model 1). However, a significant two-way interaction between violence exposure and OXTR genotype was observed; children exposed to violence with the GG genotype had shorter bTL than A allele carriers (Table S3; Model 2; $\beta = -0.044$; $P = 0.037$), and non-exposed children with the GG genotype had longer bTL than the A allele counterparts ($t = -3.03$; $p = 0.004$). A three-way interaction between violence exposure, OXTR and child sex was also present (Table S3; Model 3; $\beta = 0.125$; $P = 0.002$). When explored further, GG boys exhibited shorter bTL when exposed to violence, but longer bTL in a non-exposed environment ($t = 0.397$; $p = 0.001$). There were no significant differences in bTL in girls (data not shown).

4. Discussion

Consistent with previous studies, violence exposure was directly associated with externalizing behavior. However, despite our hypothesis, there was no direct effect of violence on diurnal cortisol or bTL (Theall et al., 2017; Moylan, 2010; Suglia, 2010 Moylan, 2010; Suglia, 2010). Genotype did not moderate the association between violence and externalizing behavior, but did moderate the association between violence and both cortisol and bTL. A allele carriers (e.g. AA or AG) did not differ in cortisol or bTL as a function of violence exposure.

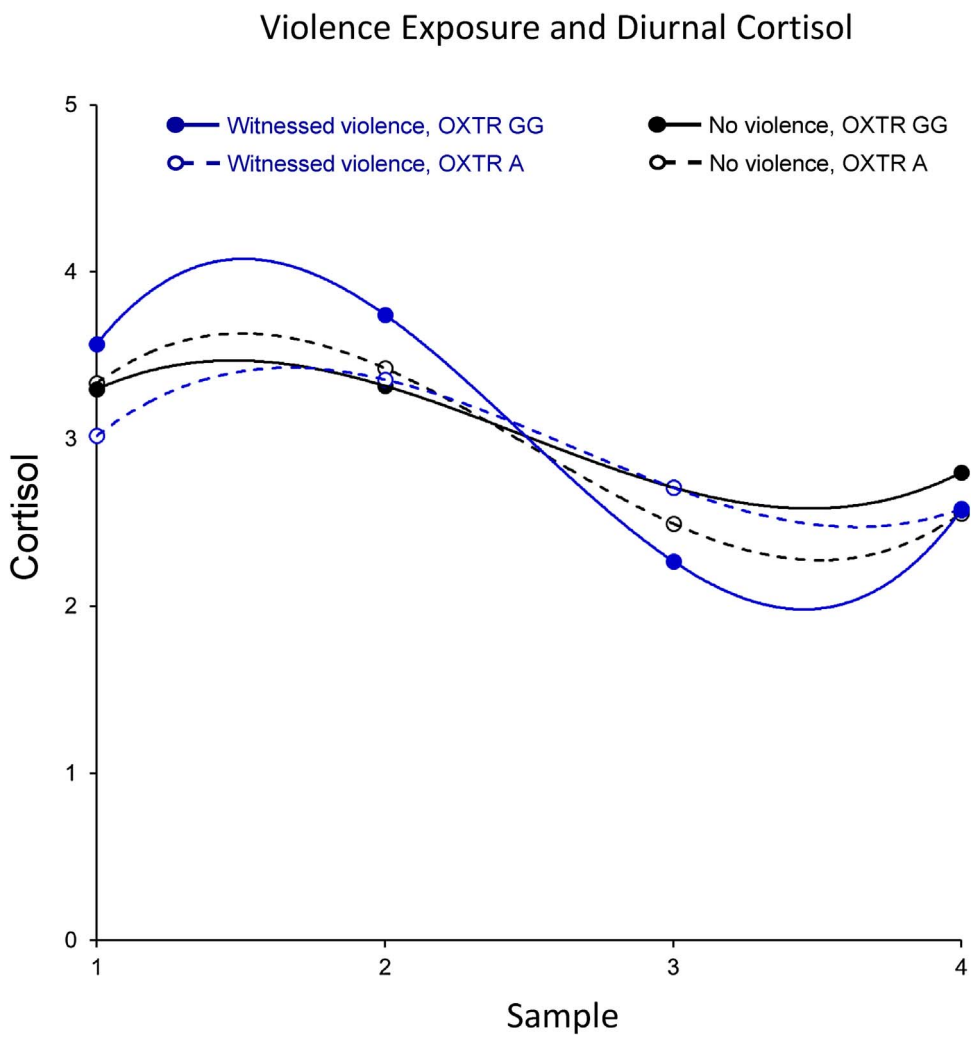

Fig. 2. Violence exposure, OXTR, and time since waking from 61 participants (N = 460 observations) predicted cortisol across the day at trend level.

However, in children with the GG genotype, exposure to violence was associated with a steeper diurnal cortisol rhythm and significantly shorter bTL compared to children with the same genotype who were not violence-exposed and to their A allele counterparts (Fig. 3).

When accounting for sex differences, OXTR allele status did not interact with sex to predict externalizing behavior. However, sex moderated the association between violence exposure and both cortisol and bTL. Specifically, an interaction with genotype was detected in only boys for these outcomes. GG boys had shorter bTL and steeper cortisol rhythm with violence exposure, but longer bTL and flatter cortisol rhythm in the absence of violence compared to A allele carriers, a pattern suggestive of the model of differential susceptibility (Belsky and Pluess, 2009). This theory posits certain genotypes do not confer risk per se, but rather contribute to an individual's susceptibility to the environment, for better or worse. Certain individuals have heightened susceptibility to the negative impacts of an adverse environment *and* the beneficial impacts of a supportive environment.

Oxytocin has an established role in social interaction and moderates the impact of social support, or lack thereof, on a range of outcomes (Heinrichs, 2003; Heinrichs, 2009; Fand et al., 2014; Lucht et al., 2009). The OXTR rs53576G allele has been linked to increased social sensitivity, a factor that is likely protective in positive environments, but potentially confers increased risk in negative environments (Bartz, 2011). Children exposed to violence, particularly violence directed at them or close family, who are more sensitive to social support because of OXTR genotype, may be at heightened risk, which is consistent with our finding of shorter bTL and steeper cortisol rhythm. These same children, if not exposed to violence, may preferentially benefit from a positive social environment. Our findings add to the existing literature that reports heightened sensitivity to social environment in those with GG genotype; however, this sensitivity appears to be outcome-specific (Bakermans-Kranenburg and van IJzendoorn, 2014; Smearman et al., 2016; Hostinar and et al, 2014). The socio-affiliative role of oxytocin may influence the efficacy of social support as well as the desire to seek out support. As cortisol regulation has been associated with an individual's desire to seek social support, our findings suggest that individuals with the GG genotype are more affected by the lack of support often associated with violent environments (Chen et al., 2011; Hill et al., 1996).

In response to NIH recommendations and previous reports of sex differences in our outcomes, we tested how our findings relate to the sex of the child. The main effect of violence exposure on increased externalizing behavior, without genotype, was driven by the girls ($\beta = 8.681$; $P = 0.024$), while no significant effect was found in the boys. Violence exposure and OXTR genotype predicted cortisol and bTL for boys only. Taken together, our results suggest that the impact of violence for girls is manifested more behaviorally, while for boys, the association is at the physiologic and molecular level. These data may suggest heightened salience of social support, independent of genotype, for female youth (Jackson and Warren, 2000; Powers et al., 2009; Antonucci and Akiyama, 1987). While our results differ from past literature where violence exposure is associated with increased exter-

Fig. 3. The impact of violence exposure on TL (N = 76). Violence exposure was not significantly associated with shorter TL (A), but was moderated by OXTR genotype, whereby GG genotype had shorter TL when exposed to violence and longer TL when not exposed. (B).*$P < 0.01$† P < 0.1

nalizing behavior in males and steeper cortisol rhythm in females, the results of interactions across outcomes suggest that future studies should consider sex and genetic variation as a potential source of between-individual differences (Deater-Deckard and Dodge, 1997; DeSantis, 2007).

This study had several strengths. First, subjects were propensity score matched for a variety of potential confounders and covariates, providing enhanced power and ability to disentangle effects of direct/observed violence. Second, this sample was a community recruited cohort that, while expected to be at risk, was not selected for psychopathology. As such, our findings may have broader generalizability. Last, we demonstrate a complex effect of violence across behavioral, physiologic, and cellular outcomes, where both sex and genotype lead to individual differences.

Despite the unique features of study, there are limitations. No direct effects were found between violence and cortisol or bTL, which may be the consequence of sample size. Genotype did not appear to moderate the association between externalizing behavior and violence exposure. The lack of genetic moderation is likely reflective of the greater complexity of the multiple genetic, biologic, and environmental factors that contribute to behavior. Given the constraints of sample size and concerns about multiple testing, we did not test a mediation model, particularly given the challenges associated with our sex differences. When parsed by sex, the sample size diminished further, suggesting sex differences may be more robust with a larger population. Furthermore, report of the child's exposure to violence was through maternal report, which is subject to bias. The study did not capture either frequency of exposure or the age at which exposure occurred, highlighting the need for more detailed examination in future larger studies. Violence exposure was described as violence inflicted on the child or on a "loved one," and did not specify the relationship of that loved one to the child. Additional ecological factors, such as family structure and parenting behavior, which were not tested in these analyses, may play consequential roles in the impact of violence exposure (Pachter et al., 2006; Caughy and O'campo, 2006). Lastly, given evidence of racial differences in violence exposure, TL, and neuroendocrine systems, as well as the small sample of available white participants in the larger study (N = 12), the cohort was restricted to Black participants. While this protects against unanticipated racial confounding, the approach limits generalizability across racial groups.

4.1. Conclusions

Despite recognition that exposure to violence, particularly for children, is associated with a broad array of negative outcomes, little progress in understanding the mechanistic pathways has been made (Calvete and Orue, 2013). By exploring the effects of environment across domains, implementing interventions capable of mitigating all the negative effects becomes pertinent. Our results highlight the cross-domain impact of violence and indicate that molecular pathways related to oxytocin may have buffering effects on physiologic and cellular pathways. Our results further suggest that the oxytocin pathway, known to be influenced by social interactions and previously associated with behavior, HPA axis function, and TL, is entwined with the biological embedding of violence (Karb, 2012; Drury et al., 2012). Larger studies that examine social support or family structure, and integrate genotype, or direct measures of oxytocin levels, are needed to define these complex pathways. Our results suggest that although violence exposure negatively impacts males and females, the behavioral, physiologic, and cellular manifestations differ by genotype and sex. Prevention and intervention efforts that only examine behavioral outcomes and do not specifically explore biological and cellular markers may not adequately address residual underlying biological scars. Exploration of cross-domain outcomes with attention to genetic moderators may better predict at-risk children, as well as those expected to respond to interventions permitting personalized treatment plans.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijdevneu.2017.03.009.

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