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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.