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ARTICLE

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A developmental origins perspective on the emergence of violent behavior in males with prenatal substance exposure

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ABSTRACT

Children with prenatal substance exposure are at increased risk for externalizing behavior problems and violence. However, the contribution of early life experiences for placing these individuals at risk is not well understood. Utilizing a sample of 1,388 children with prenatal substance exposure from the Maternal Lifestyle Study, we attempt to shed light on these contributing factors by examining the impact of infant temperament, maternal sensitivity, and early life stress on the expression of violent behavior at ages 12 through 14 years. Males may be more at risk for increases in violent behavior in early adolescence through a number of early life experiences, such as variability in responses to maternal flexibility and engagement related to individual differences in temperament, as well as exposure to early adversity. Comparing two prevailing developmental theoretical frameworks, deficit models and differential susceptibility, we aim to understand the developmental origins of violent behavior in males by identifying children who may be most susceptible to early caregiving experiences.

KEYWORDS

early life stress, prenatal substance exposure, sex differences, temperament, violence

RESUMEN

Los niños expuestos prenatalmente a sustancias se encuentran bajo un mayor riesgo de problemas de externalización de conducta y de violencia. Sin embargo, la contribución de las experiencias de la temprana vida para clasificar a estos individuos como bajo riesgo no es bien comprendida. Con el uso de un grupo muestra de 1,388 niños del Estudio de Estilo de Vida Materno, los cuales habían estado expuestos prenatalmente a sustancias, intentamos dar claridad a la contribución de estos factores por medio de examinar el impacto que tienen el temperamento infantil, la sensibilidad materna, y el estrés de la temprana vida en la expresión de conducta violenta a la edad de 12 a 14 años. Los varones pudieran estar bajo un mayor riesgo de aumento en cuanto a conducta violenta en la temprana adolescencia por medio de un número de experiencias tempranas en la vida, tales como la variabilidad de las respuestas a la flexibilidad y participación maternas relacionadas con las diferencias individuales en el temperamento, así como también el estar expuestos tempranamente a la adversidad. A través de la comparación de dos prevalentes marcos teóricos del desarrollo, modelos de déficit y la susceptibilidad diferencial, nos proponemos comprender los orígenes del desarrollo de la conducta violenta en varones por medio de identificar niños que pudieran ser más susceptibles a las experiencias tempranas de cuidado.

PALABRAS CLAVES

violencia, estar expuesto prenatalmente a sustancias, diferencias de sexo, temperamento, estrés en la temprana vida

RÉSUMÉ

Les enfants ayant été exposés à la drogue ou à d'autres substances nocives avant la naissance sont à un risque accru de problèmes de comportement d'externalisation et de violence. Cependant la contribution qu'ont certaines expériences de la vie précoce au fait de mettre ces enfants à risque n'est pas bien comprise. En utilisant un échantillon de 1388 enfants ayant été exposés à la drogue avant la naissance, de l'étude sur le style de vie maternel *Maternal Lifestyle Study*, nous essayons d'éclairer ces facteurs qui contribuent en examinant l'impact du tempérament du nourrisson, la sensibilité maternelle, et le stress de vie précoce sur l'expression du comportement violent aux âges de 12 à 14 ans. Les hommes sont plus à risque d'augmentations de comportement violent dans la jeune adolescence au travers d'un nombre d'expériences de vie précoces, tels que la variabilité dans les réactions à la flexibilité maternelle et l'engagement lié à des différences individuelles dans le tempérament, ainsi que l'exposition à une adversité précoce. En comparant deux structures développementales théoriques qui prévalent, des modèles de déficit et une susceptibilité différentielle, nous nous donnons pour but de comprendre les origines développementales du comportement violent chez les hommes en identifiant les enfants qui pourraient être les plus susceptibles aux expériences précoces.

MOTS CLÉS

violence, exposition prénatale aux drogues ou à d'autres substances novices, différences de sexe, tempérament, stress de vie précoce

ZUSAMMENFASSUNG

Kinder mit pränataler Substanzexposition sind einem erhöhten Risiko für externalisierende Verhaltensprobleme und Gewalt ausgesetzt. Der Beitrag der frühen Lebenserfahrungen zur Gefährdung dieser Individuen ist jedoch nur unzureichend erforscht. Anhand einer Stichprobe von 1.388 Kindern mit pränataler Substanzexposition aus der „Maternal Lifestyle Study" versuchen wir neue Erkenntnisse über diese beitragenden Faktoren zu gewinnen, indem wir den Einfluss vom Temperament des Säuglings, von der mütterlichen Sensitivität und vom Stress in den frühen Lebensphasen auf den Ausdruck von gewalttätigem Verhalten im Alter von 12 bis 14 Jahren untersuchen. Männer sind möglicherweise für eine Zunahme des gewalttätigen Verhaltens in der frühen Adoleszenz stärker gefährdet durch eine Reihe früher Lebenserfahrungen, wie z.B. durch die Variabilität der Reaktionen auf die mütterliche Flexibilität und das mütterliche Engagement im Zusammenhang mit individuellen Unterschieden im Temperament sowie durch die Exposition gegenüber frühen Widrigkeiten. Anhand eines Vergleichs der zwei vorherrschenden entwicklungstheoretischen Rahmen – den Defizitmodellen und der „Theorie der unterschiedlichen Empfänglichkeit" („differential susceptibility") – wollen wir die entwicklungsbezogenen Ursprünge gewalttätigen Verhaltens bei Männern verstehen, indem wir Kinder identifizieren, die für frühkindliche Pflegeerfahrungen am anfälligsten sein könnten.

STICHWÖRTER

Gewalt, pränatale Substanzexposition, Geschlechtsunterschiede, Temperament, Stress in frühen Lebensphasen

抄録

胎児期に薬物にさらされた子どもは外在化問題行動と暴力に関するより高いリスクをもつ。しかしながら、早期の体験がどのようにこの子らの危険に寄与するかはあまり理解されてはいない。母親のライフスタイル研究(MLS) から胎児期に薬物にさらされた1388人の子どものデータを用いて、 12 歳から 14 歳にかけて、暴力行動で感情表出をした子どもの、乳児期の気質・母親の感受性・早期のストレスの影響を調査した。それにより寄与する要因に光を与えようと試みた。男性は、早期の逆境体験とともに、例えば、気質の個人差に関連し、母親の柔軟性と子どもへの関わりへの反応の仕方のかわりやすさを人生早期に多く体験することで、前期思春期に暴力行動が増加するリスクが高まる。今中心的な 2 つの発達理論的枠組みである欠損モデルと差次感受性を

比較し、早期の養育体験の影響を最も受けやすい子どもを同定することで、男性の暴力行動の発達起源について理解することを目的とする。

キーワード
暴力, 胎児期の薬物曝露, 性差, 気質, 早期のストレス

摘要
接觸產前物質的兒童, 其外化行為問題和暴力的風險增加。然而, 學者尚不清楚早期經歷如何增加這些人的風險。我們利用來自母親生活方式研究的1,388名接觸產前物質的兒童樣本, 通過檢查嬰兒氣質、母親敏感性和早期生活壓力對12歲至14歲暴力行為的影響, 來闡明這些因素。通過一系列早期經歷, 如因孩子個別氣質差異影響母親的靈活性和參與, 以及早期逆境的風險, 可能會令男性在青春早期的暴力行為增加。通過比較兩種流行的發展理論框架, 缺陷模型和差異易感性模型, 我們旨在通過識別最容易受到早期護理經歷影響的兒童, 來了解男性暴力行為的發展起源。

關鍵詞
暴力, 產前暴露, 性別差異, 氣質, 早年生活壓力

ملخص
يواجه الأطفال المعرضين للمواد الضارة ما قبل الولادة مخاطر متزايدة فيما يتعلق بمشاكل السلوك الخارجية والعنف. ومع ذلك ، فإن إسهام تجارب الحياة المبكرة في تعريض هؤلاء الافراد للخطر لم يتم فهمه بشكل شامل من خلال الدراسات السابقة. تم استخدام عينه من 1,388 طفل تعرضوا لمواد ضارة قبل الولادة. هذه العينة تم الحصول عليها من دراسة كبيرة عن أسلوب حياة الأمهات . ومن خلال هذه العينة نحاول تسليط الضوء علي هذه العوامل المساهمة من خلال دراسة تاثير مزاج الرضع ، وحساسية الام ، والإجهاد العصبي المبكر في الحياه علي التعبير عن السلوك العنيف في الاعمار من 12 إلى 14. قد يكون الذكور أكثر عرضه لخطر زيادة السلوك العنيف في مرحله المراهقة المبكرة من خلال عدد من تجارب الحياة المبكرة ، مثل التباين في الاستجابات لمرونة الأمهات والاختلافات الفردية في المزاج ، وكذلك التعرض لمحنة مبكرة. وقد قمنا بمقارنة بين اثنين من الأطر النظرية السائدة الخاصة بالنمو ، ونماذج العجز والقابلية المتفاوتة للتعرض للمخاطرة ، وذلك بهدف الوصول إلى فهم أصول تطور السلوك العنيف في الذكور من خلال تحديد الأطفال الذين قد يكونوا أكثر عرضة لتجارب الرعاية المبكرة. .

الكلمات الرئيسية
العنف, التعرض للمواد قبل الولادة, الاختلافات بين الجنسين, المزاج العام, الإجهاد العصبي المبكر

With more than 1.2 million violent crimes occurring in the United States in 2016 alone (U.S. Department of Justice, Federal Bureau of Investigation [FBI], 2017), violent behavior poses a significant problem for society. Efforts on understanding and treating violence have largely been geared toward adolescent and adult criminal populations, at a time when behavior may be more resistant to treatment. Studying the early-in-life origins of violence may provide insight into developmental factors that contribute to violent proclivities and pave the way for research on higher efficacy prevention and intervention programs. One population that may be at an elevated risk for violence, in part due to their exposure to high levels of early life stress, is children with prenatal substance exposure. However, these children may differ in their susceptibility to early life experiences. Considering biological predispositions in combination with the early environment may provide more insight into developmental pathways that lead to violence among children with prenatal substance exposure.

1 | PRENATAL SUBSTANCE EXPOSURE AND VIOLENT BEHAVIOR OUTCOMES

Prenatal substance exposure is associated with detrimental effects on brain development (e.g., Rivkin et al., 2008; Thompson, Levitt, & Stanwood, 2009), which may be one mechanism underlying risk for later behavior problems, including aggression. Another contributing factor may be that these children also are exposed to high levels of early life stress, which is by itself a risk factor for maladaptive outcomes (e.g., Shonkoff, Garner, & the Committee on Psychosocial

Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section on Developmental and Behavioral Pediatrics, 2012). Children with prenatal substance exposure are disproportionately more likely to have a caretaker who is depressed, be exposed to a violent home and neighborhood, and experience changes in caregiving (Bada et al., 2011). The combination of prenatal substance exposure and early adversity amplifies the likelihood of exhibiting increases in behavioral dysregulation over time, including increases in internalizing and externalizing symptoms and delinquent acts (Fisher et al., 2011). There are two dominant theoretical frameworks that have been used to examine how prenatal substance exposure could lead to risk for a wide range of poor outcomes: the deficit model and the differential susceptibility hypothesis.

1.1 | Deficit model

Deficit models (e.g., cumulative risk: Evans, Li, & Whipple, 2013; Lupien et al., 2006; McEwen, 1998; McEwen & Stellar, 1993) have been the prevailing framework for studying the development of psychopathology. These theoretical approaches examine the effects of stress from the perspective that conditions of adversity make one vulnerable to disease-based outcomes such as deficits in cognition and behavior. Deficit models infer that treatment methods should mend resulting impairments and that intervention techniques should strive to improve damaging environmental conditions.

There is an abundant literature demonstrating that children with prenatal substance exposure are more at risk for later behavior problems and deficits in cognitive functioning, language development, and academic achievement (for extensive reviews, see Behnke & Smith, 2013; Lester & LaGasse, 2010). Extant studies tend to examine prenatal substance exposure from a deficit model, considering prenatal substance exposure as a vulnerability that would add to the developing child's risk of negative outcomes such as cognitive and emotional developmental impairments. For example, prenatal substance exposure has been predictive of impaired newborn neurobehavioral outcomes, lower IQ, and less adaptive behavior (Liu et al., 2010). Many studies have linked prenatal substance exposure to problem behavior such as impulsivity, inattention, and hyperactivity (Goldschmidt, Day, & Richardson, 2000; Nanson & Hiscock, 1990; Rosen & Johnson, 1985; Thapar et al., 2003) as well as externalizing behavior, disrupted school experiences, delinquent and criminal behavior, and high rates of substance abuse (Bada et al., 2007; Streissguth et al., 2004). Prenatal exposure to alcohol has been related to externalizing, aggressive, and delinquent behavior (Sood et al., 2001) whereas tobacco exposure has been connected to conduct disorders and violent offending (Brennan, Grekin, & Mednick, 1999; Olds, 1997).

This model has been beneficial in helping to chart the behavioral and cognitive trajectories of children prenatally exposed to substances as well as understanding deleterious effects on the brain. This model also has been useful as a framework in research that aims to identify characteristics of resilient individuals, or those seemingly less impacted by environmental stressors, with hopes of enhancing these protective factors in vulnerable persons. However, a newer theoretical framework has suggested that there may be more complexity in understanding how individuals respond to environmental conditions.

1.2 | Differential susceptibility hypothesis

The differential susceptibility hypothesis purports that biological factors (i.e., temperament, genes, physiological reactivity) predispose individuals to be more susceptible to their environment, "for better or for worse" (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007). In other words, there may be some children who are more susceptible to early life stress or prenatal substance exposure than are others. Therefore, it may be better to think of children previously viewed as "vulnerable" as "susceptible," or displaying higher degrees of plasticity (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011). These children may be more responsive to their environments, showing the *for worse* outcomes when exposed to early adversity and the *for better* outcomes when in supportive environments. A separate, distinct group of children seems insensitive to environmental stress and has similar behavioral outcomes regardless of rearing conditions (Belsky & Pluess, 2009; Conradt, Measelle, & Ablow, 2013).

Studies have begun to explore differences in susceptibility in children with prenatal substance exposure (Conradt et al., 2016; Derauf et al., 2011). We know that children with prenatal substance exposure are more likely to be born into adverse environments with higher levels of early-life stress as compared to their nonexposed counterparts; understanding how children differ in their responses to these stressors, for better or for worse, may provide insights into why some children are at a higher risk for developing violent propensities. There are three main indices of susceptibility: genetic susceptibility, behavioral susceptibility (e.g., temperament), and physiological susceptibility (Belsky & Pluess, 2009). For example, Conradt et al. (2016), in a study from this current sample, examined the physiological index of susceptibility in infants at 1 month of age. They found that infants who exhibited more respiratory sinus arrhythmia reactivity *and* who were raised by a caregiver who experienced high levels of stress and psychopathology exhibited more behavior dysregulation at age 3 years. In comparison, infants who were less physiologically reactive and who had less stressed caregivers exhibited less behavior dysregulation at age 3 (Conradt et al., 2016).

There have been few tests of behavioral indices of susceptibility in children with prenatal substance exposure. This is surprising, given that one of the most replicated susceptibility factors is a difficult, or negative, infant temperament (Belsky & Pluess, 2009). When children with difficult temperaments are raised in supportive, nurturing environments, they sometimes have the best outcomes, surpassing the outcomes of children with easy temperaments reared in similar conditions (Belsky & Pluess, 2009). However, infants with difficult temperaments reared in high stress conditions have been shown to have the worst outcomes and are at higher risk for developing deficits in academic and social competencies, teacher–child relations, peer status, and externalizing behavior (Belsky & Pluess, 2009; Bradley & Corwyn, 2008; Stright, Gallagher, & Kelley, 2008**;** Pluess & Belsky, 2009; van Aken, Junger, Verhoeven, van Aken, & Dekovic, 2007). For instance, van Aken et al. (2007) found that 16- to 19-month-old boys who were temperamentally difficult were more susceptible to maternal insensitivity, hostility, and intrusiveness, which resulted in increases of externalizing behavior. Similarly, Bradley and Corwyn (2008) found that 6-year-old boys and girls with difficult temperaments were more susceptible to maternal sensitivity, showing the highest levels of externalizing behavior with insensitive parenting, but the lowest levels of externalizing behavior with sensitive parenting.

These examples point to the importance of considering the interaction between child temperament and parenting factors. Most research to date has been built on the premise that the effects of parenting are equal for children, which neglects that the effectiveness of parenting may depend on the bidirectional relationship between individual child traits (e.g., temperament) and parenting style (Belsky et al., 2007). These findings support the differential susceptibility hypothesis in that some children may be more susceptible to the effects of parenting, such as maternal sensitivity, than may others.

Since males are responsible for a significantly disproportionate amount of violent behavior, it is critical to consider that males may be more sensitive to these developmental experiences earlier in life. There may be sex differences in infant temperament, as found by (Weinberg, Tronick, Cohn, & Olson 1999). At 6 months of age, boys were more likely to express anger than were girls and depended on feedback from mothers to regulate emotions whereas girls showed more self-regulation abilities. Boys also were found to be more emotionally expressive than were girls, showing higher rates of both positive and negative emotions. In addition, more negative interactions are observed between mother–son dyads (vs. mother–daughter dyads) when mothers experience high levels of depressive symptoms (Weinberg, Olson, Beeghley, & Tronick, 2006). These findings have suggested that males may be particularly susceptible to the influence of maternal mood.

Exploring who may be most at risk for violent behavior outcomes is necessary to account for gaps in the prenatal substance exposure literature. One important gap concerns the need to account for the effects of early life stress (e.g., poverty, maternal depression) in addition to the effects of the drug on violent behavior. Large sample sizes are necessary to provide sufficient power to detect the differential effects of prenatal substance exposure above and beyond the impact of early life stress. Second, many studies have examined prenatal substance exposure retrospectively, limiting the reliability of the reporting. Third, there are few studies that have examined behavioral indices of susceptibility in children with prenatal substance exposure, which may provide pertinent information on the contribution of individual differences to violent outcomes. Accounting for these gaps may further our understanding of why only a subset of at-risk individuals exposed to similar circumstances go on to commit violent offenses.

2 | PRESENT STUDY

This study will examine sex differences in violent behavior outcomes for individuals with prenatal substance exposure. First, we will document changes in violent behavior across development, separately for males and females. Second, we will examine early life predictors of violence for both males and females. Deviating from a deficit model, where adverse experiences lead to accumulated risk for poor developmental outcomes, and shifting toward understanding how individuals differ in their susceptibilities to early-life experiences may provide insight into the development of violent behavior. Utilizing a sample of 1,388 children with prenatal substance exposure from the Maternal Lifestyle Study, we will attempt to advance understanding on how males may be more susceptible to developmental experiences that place them at risk for violent outcomes.

3 | METHOD

3.1 | Study participants and sites

The Maternal Lifestyle Study is a multisite, longitudinal study designed to examine the effects of prenatal cocaine exposure and associated stressors on child development. Participating study locations were Brown University (Providence, RI), University of Miami (Miami, FL), University of Tennessee (Memphis, TN), and Wayne State University (Detroit, MI). Mother–infant dyads were recruited for participation in the hospital following delivery (for details regarding inclusionary and exclusionary criteria, see Lester et al., 2002). Mothers were screened for illicit drug use (tobacco, marijuana,

alcohol, cocaine, opiates) during pregnancy through meconium assays and self-report. Of 19,079 participants screened, 16,988 were found to be eligible for the study, with 11,811 consenting for participation. Mothers were approached in the hospital following delivery, informed consent was obtained, and they were interviewed for history of smoking, alcohol use, and drug use during pregnancy and in the last year. Meconium was collected from the newborn to conduct toxicology screens for cocaine or opiate metabolites. Families were selected for the exposed group (i.e., maternal report of cocaine or opiate use during pregnancy or gas chromatography–mass spectrometry confirmation of presumptive positive meconium screens for cocaine or opiate metabolites) or the comparison group (i.e., maternal denial of cocaine or opiate use during the pregnancy and a negative enzyme multiplied immunoassay meconium screen for cocaine and opiate metabolites). If a woman denied use of cocaine during pregnancy, but mass spectrometry results were positive for cocaine exposure, then the child was considered cocaine-exposed. Exposed and comparison newborns were group matched on race, sex, and gestational age within each study site. Background substances associated with cocaine use (alcohol, tobacco, and marijuana) were present in both groups; thus, most participants were poly-substance-exposed. Enrollment in the longitudinal portion of the study began at 1 month ($n = 1{,}388$) and continued through 16 years of age. Children participating in the study were identified by their parents as African American (77%), Caucasian (16%), Hispanic (6%), and other racial background (1%). An NIDA Certificate of Confidentiality was acquired by each study site to ensure confidentiality to participants regarding maternal drug use. All study sites were approved through the Institutional Review Board, and participants gave consent prior to participation.

3.2 | Measures

Prenatal substance exposure was measured through self-report at the hospital postdelivery, where mothers were interviewed regarding their smoking, drinking, and substance use over the past year, including pregnancy. Toxicology screens also were completed on newborn meconium samples to screen for the presence of cocaine and opiate metabolites. The Caretaker Inventory of Substance Use (CISU; Shankaran et al., 1996) was administered when the child was 4 months of age. The CISU measures frequency and duration of use for tobacco, marijuana, alcohol, cocaine, and opiates. Since the study was designed to study the effects of cocaine exposure, 658 cocaine-exposed infants and 730 non-cocaine-exposed infants were included. There is a high likelihood that women who report substance use during pregnancy can be characterized as polysubstance users (Birnbach, Browne, Kim, Stein, & Thys, 2001); as such, many infants in both groups (cocaine-exposed and non-cocaine-exposed) were exposed to multiple substances such as tobacco, alcohol, marijuana, and opiates. Only a smaller group of infants (21.3%) was characterized as not having any prenatal substance exposure. Through utilization of these self-reports and meconium samples, substance use was quantified dichotomously (0 = *no*, 1 = *yes*) by assigning a point per affirmative response, which is a frequently used method to examine prenatal substance exposure outcomes (Fisher et al., 2011). A summative index was subsequently created with a 0 (*no substance use*) to 5 (*endorsed use of each substance*) scale to indicate whether mothers had partaken in the following substances: tobacco, alcohol, marijuana, opiates, and cocaine.

Infant temperament was operationalized through a modified version of Rothbart's Infant Behavior Questionnaire (IBQ; Kunkel & Brown, 1993; Rothbart, 1981), which was administered to the mother when child was 4 months old. A variety of behavioral events was identified by a yes/no categorization; if yes, participants provided follow-up information on a 5-point response scale ranging from 1 (*never*) to 5 (*always*). Summary scores were obtained for activity level, smiling and laughter, distress and latency to approach sudden or novel stimuli, distress to limitations, soothability, and duration of orienting. Factor analysis was utilized to generate an "easy" temperament profile (smiling and laughter, soothability, and duration of orienting) and a "difficult" temperament profile (distress and latency to sudden approach and novel stimuli, distress to limitations).

3.2.1 | Maternal sensitivity at 1 month

Mother–infant dyads were recorded while completing a bottle-feeding task (LaGasse et al., 2003) at 1 month (42–46 weeks) of age; 46 mothers who exclusively breast-fed were not invited to participate in this specific task. Mothers were asked to withhold feeding, when possible, until arrival at the clinic site. Videos were coded (Coders were blinded to prenatal substance exposure status.) for behaviors of *maternal engagement and flexibility* (the mother's response to feeding cues from infant and quality of maternal attentiveness) as well as *maternal stimulation* (frequency of behaviors, e.g., maternal vocalizations, caressing/stroking, kissing).

Early adversity was examined using a summative risk index that included nine risk factors from birth to age 3. Cumulative risk models surmise that combinations of risk factors are stronger predictors of developmental outcomes than is studying single risk factors, as these risks are not likely to occur in isolation in substance-exposed populations (Carta et al., 2001). Individual risk factors, originally a continuous scale or a count score, were dichotomized to generate an overall risk index (0 = *no*/*none*, or 1 = *yes*/*one or more*). Cutoffs were established on previous research suggesting that high values on these risk indices are representative of valid risk for the development of problem behavior (Fisher et al., 2011;

Sheinkopf et al., 2007): (a) postnatal substance use of cocaine, opiates, tobacco, alcohol, or marijuana as reported by the mother through the Year 3 assessment; (b) chronic poverty status defined as income below $10K for a minimum of 75% of the visits; (c) low social status calculated via the Hollingshead Index of Social Position (Hollingshead, 1975) utilizing education and occupation scores averaged over yearly visits and scored as 1 *SD* or more below the mean; (d) any changes in primary caretaker, reviewed yearly; (e) any record of sexual or physical abuse as reported by caregivers; (f) caregiver depression of 1 *SD* or greater above the mean for average depressive symptoms on the Beck Depression Inventory (Beck & Steer 1993), administered annually to the caregiver; (g) caregiver psychological distress of 1 *SD* or greater above the mean for total psychological symptoms on the Brief Symptom Inventory (Derogatis 1993), administered annually to the caregiver; (h) poor-quality home environment of 1 *SD* or more below the mean on the Home Observation Measurement of the Environment (Caldwell & Bradley, 1984, 2003), appraised when the child was 10 months old through completion of a home visit; and (i) any history of Child Protective Services involvement through age 3 years for the target child, assessed yearly by caregiver report.

3.2.2 | Violent behavior at 12, 13, and 14 years

The outcome variable of violence was operationalized through use of Things That You Have Done (Elliot, Ageton, & Huizinga, 1985), which is a 27-item child-report questionnaire measuring the child's involvement in delinquent activities over the past year. We used the "crimes against others" subscale, which included hitting, slapping, or shoving other kids or getting into a physical fight; threatening to hit someone to get something; attacking someone; throwing objects such as rocks and bottles at people; and having been involved in a gang fight. We examined violent behavior outcomes at ages 12, 13, and 14.

3.3 | Statistical analyses

We first ran unconditional models predicting change in violent behavior from ages 12 to 14, separately for males and females. Model fit was evaluated based on the comparative fit index and root mean square error of approximation. Covariates were selected based on published literature and statistical evidence. We included prenatal substance exposure (prenatal cocaine, alcohol, tobacco, opioid, and marijuana exposure), indices of early adversity, race and ethnicity, and study site in all analyses. Missing data (n = 177 boys, n = 135 girls) were accounted for using multiple imputation. All statistical analyses were conducted using Mplus version 7.0 (Muthén & Muthén, 2012). We tested for significant differences at $p < .05$.

TABLE 1 Demographic characteristics of males versus females

	Males (n = 550)	Females (n = 526)
Prenatal exposure to cocaine (1 = *exposed*)	.43 (.50)	.45 (.50), n.s.
Prenatal exposure to opioids (1 = *exposed*)	.08 (.27)	.09 (.29), n.s.
Prenatal exposure to alcohol (1 = *exposed*)	.59 (.49)	.60 (.49), n.s.
Prenatal exposure to tobacco (1 = *exposed*)	.51 (.50)	.57 (.50), p = .02
Prenatal exposure to marijuana (1 = *exposed*)	.21 (.41)	.26 (.44), n.s.
Race: Black (%)	73.3%	80.2%, n.s.
Maternal education	1.83 (.76)	1.80 (.75), n.s.
Marital status	1.83 (.46)	1.85 (.44), n.s.
Maternal age (years)	28.40 (5.82)	28.28 (5.84), n.s.
Early adversity	2.19 (1.42)	2.29 (1.40), n.s.
Flexibility and engagement	−.03 (1.01)	.04 (.98), n.s.
Stimulation and activity level	−.02 (1.06)	.03 (.93), n.s.
Infant negative temperament	−.09 (.95)	.10 (1.05)
Infant easy temperament	.008 (.99)	−.009 (1.02)

4 | RESULTS

4.1 | Preliminary analyses

Data were examined for outliers and violations of normality. Outliers above or below 3 *SD*s from the mean were winsorized by replacing the value with the value at 3 *SD*s. Means and *SD*s for demographic characteristics and all covariates and predictors, separately for males and females, are included in Table 1. We first examined whether there were differences in amount of violent behavior, separately between males and females, at each age. Males displayed significantly more violent behavior at age 12, M_{males}= .41, SD_{males}= .71; M_{females}= .27, SD_{females}= .64; $F(1, 994) = 10.48$, $p < .001$, and age 13, M_{males}= .69, SD_{males}= .98; M_{females}= .54, SD_{females}= .94; $F(1, 990) = 6.36$, $p = .01$, but there were only marginally significant differences in violent behavior between males and females at age 14, M_{males}= .77, SD_{males}= .99; M_{females}= .67, SD_{females}= .90; $F(1, 992) = 3.02$, $p = .08$.

4.2 | Unconditional growth models

4.2.1 | Male model

We first tested for growth in violent behavior in males from ages 12 to 14 sans covariates or predictors. We found that violent behavior in males significantly increased from ages

12 to 14, $M_{\text{linear slope}} = .18$, $p < .001$. However, there was significant variability in the linear slope, $\sigma^2 = .12$, $p < .001$, indicating that some children's violent behavior increased, some decreased, and some remained the same.

4.2.2 | Female model

We also tested for unconditional growth in violent behavior in females from ages 12 to 14. We found that violent behavior in females from ages 12 to 14 significantly increased, $M_{\text{linear slope}} = .21$, $p < .001$. However, there was significant variability in the linear slope, $\sigma^2 = .17$, $p < .001$, indicating that some female children's violent behavior increased, some decreased, and some remained the same.

4.3 | Early life predictors of violent behavior

4.3.1 | Male model

We examined the following early-life predictors of violent behavior in males: prenatal exposure to cocaine, opiates, tobacco, alcohol, and marijuana, as well as early adversity, maternal flexibility and engagement, maternal stimulation and activity level, "difficult" temperament, and "easy" temperament. Given our interest in testing for differential susceptibility versus deficit model, we also tested for significant interactions between a "difficult" temperament and maternal flexibility and engagement, as well as between a "difficult" temperament and maternal stimulation. The only significant predictor on the intercept, violent behavior at age 12, was a "difficult" temperament. High levels of "difficulty" were related to higher levels of violent behavior at age 12, $b = .12$, $p = .05$. None of the other main effects or interactions were significant.

These same variables were examined as predictors of growth in violent behavior in males from ages 12 to 14. Higher exposure to tobacco prenatally was related to decreases in violent behavior from ages 12 to 14, $b = –.16$, $p = .04$. Higher levels of early adversity were related to increases in violent behavior, $b = .19$, $p = .02$. Again, there was a main effect of infant "difficult" temperament on violent behavior, with higher difficult temperament predicting decreases in violent behavior, $b = –.24$, $p = .004$. However, this main effect was qualified by a significant Difficult Temperament × Maternal Flexibility and Engagement Interaction, $b = –.05$, $p = .056$.

We probed this interaction at ±1 *SD* from the mean for difficult temperament and maternal flexibility and engagement using the online computational tools provided by Preacher, Curran, and Bauer (2006). For mothers with low levels of flexibility and engagement, there were no significant differences in change in violent behavior, regardless of infant difficult temperament (Figure 1a). Among mothers with high levels of flexibility and engagement, infants who were rated as less difficult exhibited increases in violent behavior over time,

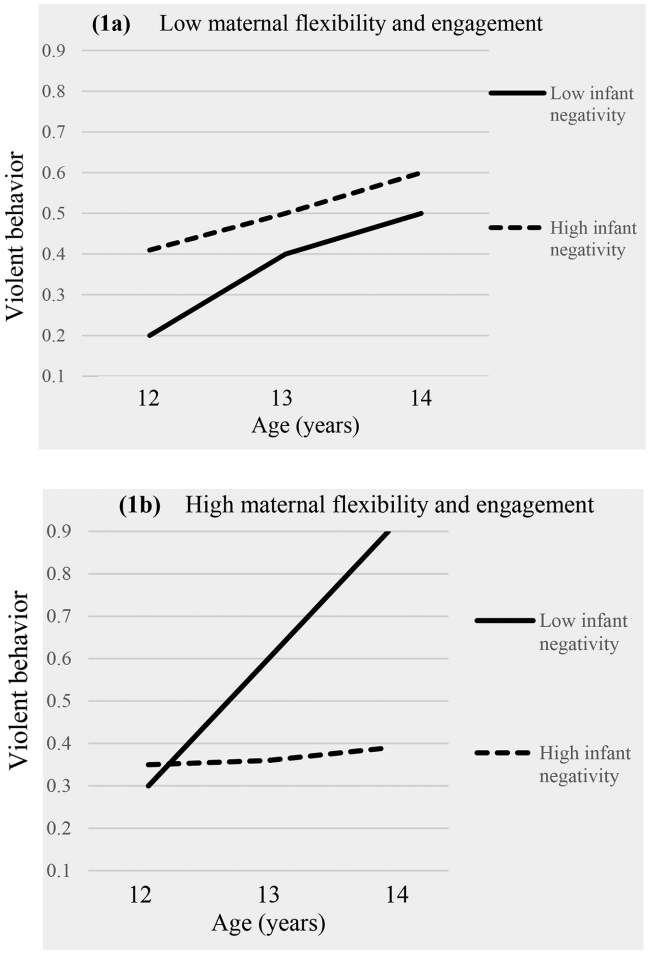

FIGURE 1 The interaction between infant negativity, maternal flexibility and engagement, and time. (a) Among mothers low on flexibility and engagement, there are no significant differences in violent behavior in males among infants, regardless of their level of temperamental negativity. Among mothers high on flexibility and engagement, there are no significant differences in violent behavior in males over time among infants rated high on negativity. (b) Among infants rated low on negativity, violent behavior increases over time

$b = .33$, $p = .002$, while infants rated high on negativity exhibited no changes in violent behavior over time (Figure 1b).

4.3.2 | Female model

We examined the same early-life predictors of violent behavior in females. The only significant predictor on the intercept, violent behavior at age 12, was maternal flexibility and engagement. High levels of maternal flexibility and engagement were related to lower levels of violent behavior at age 12, $b = –.13$, $p = .01$. None of the other main effects or interactions were significant.

These same variables were examined as predictors of growth in violent behavior in females from ages 12 to 14. Higher levels of prenatal opioid exposure were related to increases in violent behavior from ages 12 to 14, $b = .14$,

$p = .01$. Difficult temperament also was significant, with higher levels of difficult temperament predicting increases in violent behavior in females from ages 12 to 14, $b = .15$, $p = .04$. None of the interactions were significant.

5 | DISCUSSION

Utilizing a high-risk population with prenatal substance exposure, we examined infant temperament, caregiving interactions, and early life stress exposure in an attempt to identify the early childhood experiences that contribute to violent outcomes from ages 12 to 14. Leveraging a sample of over 1,300 children with prenatal substance exposure assessed from 1 month to 14 years, we had the power to detect whether these early childhood experiences and exposures were related to violent behavior approximately one decade later. While there were some exceptions (e.g., male prenatal exposure to tobacco), the findings tended to lend support to the deficit model as exposure to challenges early in life resulted in greater risk for violent behavior outcomes. The results also indicate that some boys, based on their temperamental traits, were more sensitive to the effects of maternal caregiving than were others; however, our findings did not meet evidentiary criteria for establishing a case of differential susceptibility (Belsky et al., 2007).

Overall, males engaged in more violent behavior than did females at all ages, and violent behavior increased from ages 12 to 14 years for both boys and girls. These findings are not surprising, given what is known about developmental trends in violent behavior. Nagin and Tremblay (1999) examined trajectories of externalizing behavior in males and found that physical aggression typically decreases from school-entry until adolescence, where there is a surge in aggression. Research to date has distinguished between an adolescent limited aggression and life-course persistent violent behavior (Moffitt, 1993), so these adolescent outcomes may not necessarily be predictive of adult offending.

Higher levels of tobacco exposure were related to decreased levels of violent behavior from ages 12 to 14 years in males. This finding was surprising, as it is inconsistent with literature that has found prenatal tobacco exposure to increase risk of externalizing behavior, including conduct disorder and violent behavior outcomes. These mixed findings point to the importance of studying potential moderators. Higher levels of prenatal opioid exposure were related to increases in violent behavior from ages 12 to 14 in females. This contributes to a growing body of literature on the effects of prenatal opioid exposure at a time when such information is critical given the current opioid epidemic. This is the first study to find that prenatal opioid exposure occurring in the 1990s, that included both heroin and methadone exposure, is predictive of violent behavior 12 to 14 years later, but only in females.

One mechanism linking prenatal substance exposure and violent outcomes may be neurobehavioral disinhibition. Originally developed by Tarter (2003) in an effort to characterize a group of children at risk for delinquency later in life, neurobehavioral disinhibition is an intricate disinhibitory psychopathology (Iacono, Malone, & McGue, 2008) that cannot be distinguished by a single diagnosis. There are characteristics of neurobehavioral disinhibition that have been related to risk for violent behavior, including disruptive behavior disorders, executive functioning difficulties, and poor self-regulation (Fisher et al., 2011). As one example, Lambert et al. (2013) found that executive dysfunction partially mediated the relationship between prenatal substance exposure and being arrested at age 15.

In males, but not females, higher levels of infant negativity/difficulty were related to higher levels of violence at age 12. As expected from the review of previous literature on temperament, difficult temperament could be related to a heightened risk for poor behavioral outcomes (Patterson, 1976). High levels of infant negativity also were predictive of growth in violent behavior from 12 to 14 in both males and females. For females, the direction of effect was as hypothesized: Greater infant negativity at 4 months of age was related to increases in violent behavior from ages 12 to 14. Males showed the opposite pattern of results: Greater infant negativity was associated with *lower* levels of violent behavior from ages 12 to 14. However, for males only, this main effect was qualified by a significant interaction with maternal caregiving behavior at 1 month.

For males, there appeared to be no difference in growth in violent behavior if their mothers were less flexible and engaged when interacting with them at 1 month. Both temperament groups showed increases in violent behavior from ages 12 to 14. On the other hand, males with less difficult temperaments displayed increases in violent behavior over time, but only in combination with high maternal flexibility and engagement. Males with more difficult temperament showed no increases in violent behavior over time if their mothers were more flexible and engaged when interacting with them at 1 month. For females, there were no significant interactions, but high levels of flexibility and engagement were related to lower levels of violent behavior at age 12.

These findings indicate that male infants who exhibit easy temperaments at 4 months may be more sensitive to maternal parenting practices characterized by flexibility and engagement. It may be that males are more vulnerable to the amount of stimulation in their early rearing environment. This finding contrasts with previous research that tends to show that individuals (male or female) with easy temperaments are less susceptible to environmental experiences (Belsky & Pluess, 2009; Bradley & Corwyn, 2008; Stright et al., 2008; Pluess & Belsky, 2009; van Aken et al., 2007). However, for a time period, sociocultural concerns led many developmental

researchers to neglect examining sex differences in data sets, therefore failing to account for possible individual differences.

One explanation of these findings is that males with less difficult temperaments may be exhibiting lower levels of arousal which may be overstimulated by high levels of maternal attention (flexibility and engagement). If this overstimulation persists, it may manifest as externalizing behavior problems, which could, in turn, give rise to aggressive behavior. An alternate explanation is in accordance with the sensation-seeking theory literature. This theory suggests that individuals low on arousal may prefer a stronger level of stimulation to be aroused by a stimulus, thus increasing their chances of engaging in risky behavior (Zuckerman, 2009).

Another strong predictor of increases in violent behavior in males was exposure to early adversity. Early-life stress from birth to age 3 years was related to increases in violent behavior from ages 12 to 14 years in males, but not females. The most comprehensive theory to date on the origins of sex differences in exposure to early life adversity comes from Sandman, Glynn, and Davis (2014), who proposed that there could be a viability-vulnerability trade-off that contributes to sex differences in developmental outcomes. In other words, Sandman et al. (2014) argued that exposure to early adversity in males threatens their viability, or risk for early mortality. Females are more likely to survive following exposure to early adversity, but that may lead to increased vulnerability for affective and anxiety disorders later in life (Sandman et al., 2014). We did not find support for this theory in this study, given that it appeared as though boys were more susceptible to the effects of both early adversity and maternal caregiving behaviors.

Instead, the vulnerability for males may be vulnerability for committing violent behavior in early adolescence. In this sample, males were significantly more likely to engage in violent behavior than were females, which is consistent with overall sex differences in violent crime rates. Our results suggest that one important pathway to violent behavior included both infant temperament and maternal caregiving behavior. These findings require replication before firm conclusions can be drawn, but these findings suggest that both infant temperament and caregiving behavior should be assessed by early interventionists motivated to prevent externalizing behavior.

5.1 | Limitations

There are limitations of this research. First, we cannot determine direction of effect with these data. We can in no way conclude, for example, that temperamental difficulty at 4 months causes increases or decreases in violent behavior in adolescence. Another limitation includes the assessment of maternal engagement and flexibility during a feeding task. Mothers who breast-fed were not invited to participate. Because mothers who elect to breast-feed their infants tend to show higher rates of maternal sensitivity (e.g., Britton, Britton, & Gronwaldt, 2006; Tharner et al., 2012), the task may be limited in the range of maternal behaviors observed.

It is important to consider that processes outside the scope of the study could contribute to the findings presented here. For example, Gene × Environment interactions were not examined. In addition, women in this sample were not assessed prenatally. Developmental programming, including during the prenatal period, may have explanatory power for the developmental origins of violent behavior in children with prenatal substance exposure. Prenatal programming, along with neurochemical and vasoconstrictive mechanisms, is one of three pathways through which prenatal substance exposure may impact fetal development (Lester & Padbury, 2009). Prenatal programming theory proposes that maternal environment and experiences can alter the uterine environment, triggering epigenetic changes that prime the developing infant for what the external world will be like. Developmental programming continues throughout the life span, with the early years of life likely playing an important role. When considering children with prenatal substance exposure and high levels of early-life stress, programming effects may explain variance in how children respond to early life experiences and how this relates to their subsequent developmental outcomes.

5.2 | Conclusion

In conclusion, a number of early-life experiences may place males at higher risk for the development of violent behavior. These early-life experiences include exposure to adversity and the interaction between child temperament and maternal sensitivity. Our findings underscore the importance of examining individual differences in combination with early developmental experiences to understand the mechanisms that lead to behavioral problems in adolescence. Since biological risk factors in combination with environmental conditions often provide a more complete picture than does examining main effects alone, it is imperative to consider these interactions when identifying novel treatment and intervention methods (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008).

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