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Prenatal exposure to tobacco and cannabis: Effects on autonomic and emotion regulation

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ABSTRACT

Tobacco and cannabis are often used together in pregnancy and both have effects on children's regulatory system. Yet, little is known about the impact of co-use on the development of emotion regulation at the developmentally salient age of 2 years. One pathway linking co-exposure to tobacco and cannabis to toddler regulation may be via poor autonomic regulation in infancy. In addition, substance using mothers may be more dysregulated themselves, which may have direct effects on toddler regulation, but may also affect parenting, particularly maternal sensitivity during mother-child interactions. Thus, a second pathway linking exposure to toddler regulation may be via maternal dysregulation and low maternal sensitivity. We examined a conceptual model linking prenatal exposure to toddler regulation via these two pathways in a prospective sample ($N = 247$) of mother-child dyads recruited in the first trimester of pregnancy. Results indicated significant effects of co-exposure on poor autonomic regulation in infancy, which in turn predicted poor toddler emotion regulation. Mothers who used both tobacco and cannabis displayed lower sensitivity during play interactions with their infants. Maternal sensitivity was modestly stable from infant to toddler period and was predictive of higher toddler emotion regulation. Continued postnatal exposure to tobacco was also a significant, unique predictor of lower toddler emotion regulation. Results highlight the importance of examining co-exposure effects and suggest that this common pattern of use may be associated with higher infant/toddler risks.

1. Introduction

Tobacco and cannabis are two of the most commonly used substances among pregnant women, with tobacco use rates ranging from 18% to 27% (USDHHS, 2014). These rates are even higher among young, low-income women (USDHHS, 2014). A large number of women who use tobacco also use cannabis with co-use rates as high as 45% (Chabarria et al., 2016), but little is known about the effects of co-occurring use. This is especially critical given changes in cannabis legalization and increases in cannabis potency in recent years (Calvigioni et al., 2014; Mehmedic et al., 2010).

Tobacco use in the form of cigarettes delivers significant amounts of chemical toxins to the fetus via maternal bloodstream (USDHHS, 2014). Prenatal tobacco exposure (PTE) also increases norepinephrine and dopamine concentrations (Lichtensteiger et al., 1988), as well as acetylcholine and serotonin (Slotkin et al., 2015) in the developing brain. Similarly, gestational cannabinoid exposure in rats interferes with neuronal wiring (pro-apoptotic brain signaling molecule changes, DNA fragmentation) and may cause subsequent impairments in regulatory behaviors (Downer et al., 2007; Scott-Goodwin et al., 2016). Recent brain morphology studies indicated that tobacco exposed children had cortical thinning, especially in the frontal and superior parietal cortices (El Marroun et al., 2016; Toro et al., 2008), while cannabis exposed children had thicker frontal cortices indicating altered neurodevelopmental maturation in regions involved in higher order processing (El Marroun et al., 2016). Both these alterations may also result in deficits in regulation of emotions. Indeed, there is robust evidence of the association between PTE and arousal dysregulation in the neonatal period (Espy et al., 2011; Jacobson et al., 1984; Stroud et al., 2009), a smaller literature in infancy (Wiebe et al., 2014; Schuetze et al., 2017), and a larger literature on problem behavior in later childhood (USDHHS, 2014, review). Similarly, prenatal cannabis exposure was associated with deficits in sustained attention and lower self-regulation in later childhood (Day et al., 2006; Day et al., 2011; Day et al., 1994; Fried, 2002; Willford et al., 2012). However, little is known about effects of co-occurring use of tobacco and cannabis (PTCE) on emotion regulation in early childhood. This was the major goal of the current study.

Emotion regulation was defined as a process of modulating intensity

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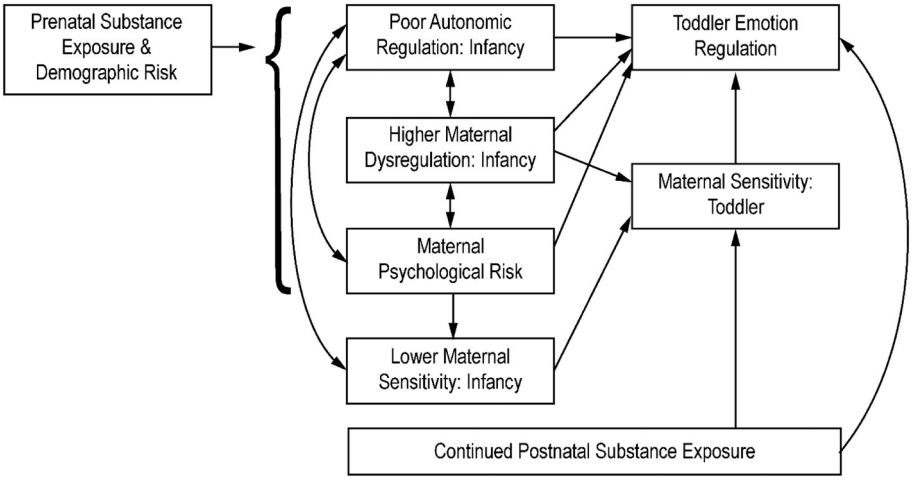

Fig. 1. Conceptual model.

and duration of affective states and related physiological processing (Morris et al., 2017). Indeed, physiological processing of affective states may play a critical predictive role in behavioral manifestations of emotion regulation. One particularly useful measure of physiological regulation is respiratory sinus arrhythmia (RSA), a measure of the high-frequency portion of heart rate variability that occurs within the frequency range at which respiration occurs (approximately 0.24–1.04 Hz for infants; Porges et al., 1996). Although RSA is multiply determined, it is believed to index activity of the parasympathetic nervous system in autonomic control of heart rate via the vagus nerve. Two commonly used indices of autonomic regulation (Porges, 1996) include RSA at rest (baseline RSA) and changes in RSA during environmental demands (RSA regulation; Bornstein and Suess, 2000; Calkins, 1997). Baseline RSA is a measure of the infant's ability to maintain physiological homeostasis during periods of minimal external stimulation. During exogenous challenges to homeostasis, activity of the parasympathetic nervous system is often reduced, allowing HR to increase, which, in effect, releases the parasympathetic brake on HR (Porges et al., 1996). RSA regulation during periods of environmental challenge is believed to reflect the infant's ability to appropriately engage or disengage with the environment (Bornstein and Suess, 2000; Porges, 1996), such that RSA is suppressed during stressful or negative emotional situations. Thus, the measurement of change in RSA from baseline in response to stress or negative affect situations may be an important index of autonomic regulation in infants and be predictive of emotion regulation at later ages.

Theories of emotion regulation highlight the importance of autonomic regulation of arousal as an important predictor of children's ability to effectively modulate emotions in challenging contexts (Beauchaine, 2001). Indeed, RSA suppression in response to affective challenges were associated with higher levels of emotion regulation and lower problem behavior, while maladaptive RSA increases in these contexts were predictive of higher behavior problems (Calkins et al., 2007; Calkins and Keane, 2004; Cho et al., 2017). Thus, one mechanism linking PTE and PTCE to toddler emotion regulation may be autonomic regulation (Baseline RSA and RSA suppression) in infancy. One major goal of this study was to examine the association between prenatal substance exposure (particularly co-exposure to tobacco and cannabis) and toddler emotion regulation (at 24 months of child age) via poor autonomic functioning in infancy (at 9 months of child age).

Although few studies examined the role of autonomic regulation as an explanatory mechanism linking co-exposure to tobacco and cannabis (PTCE) to toddler emotion regulation, there is a small, but robust literature on PTE and autonomic regulation. During early infancy, studies found higher heart rates during quiet and active sleep, lower long-term heart rate variability, and lower baseline RSA during rest among tobacco exposed infants (Franco et al., 2000; Schuetze and Zeskind, 2001; Schuetze and Eiden, 2006; Schuetze et al., 2013; Zeskind and Gingras, 2006). In later infancy, one study reported significant RSA suppression in response to negative emotion among control infants, but not among tobacco exposed infants (Schuetze et al., 2013). Thus, it is unclear if dual exposure to both tobacco and cannabis is associated with poor autonomic regulation, but given the small but robust literature on tobacco effects on infant autonomic regulation, we hypothesized this as a mediating pathway.

In addition to autonomic variables, parents are one of the most critical influences on development of emotion regulation. Mothers using tobacco and cannabis not only experience greater demographic risks, such as younger age, lower income, and single status (Chabarria et al., 2016; USDHHS, 2014), but are also at higher risk for emotional dysregulation and are at higher risk for symptoms of depression and anger/hostility (Eiden et al., 2011; Ludman et al., 2000; Massey et al., 2016). Mothers' own emotion regulation abilities and psychological risk may impact child emotion regulation via social learning processes, by impacting parenting, or through potential heritability of dispositional facets of emotion regulation. However, despite theoretical support, few studies examined parents' emotion regulation as a predictor of child emotion regulation, although studies examined the role of parents' emotion socialization of their children and psychological symptoms as predictors of child outcomes (Eisenberg and Fabes, 1992; Eisenberg et al., 1996). Parents' own emotion regulation and psychological symptoms may also impact quality of parenting, the most proximal predictor of child emotion regulation. Indeed, the capacity to regulate emotions is strongly rooted in dyadic parent-infant interactions (Schore, 1994). Empirical evidence points to the critical protective role of maternal sensitivity in the infant toddler period, which includes warmth, support, and acceptance of children and contingent responsiveness to child cues, as a proximal predictor of children's emotional and behavioral regulation across development (Feldman et al., 2011; Feldman et al., 1999; Kochanska et al., 2008). Thus, a second goal of this study was to examine the role of maternal sensitivity as an additional predictor of toddler emotion regulation (see Fig. 1).

There is some evidence that boys are more vulnerable to PTE, including stronger PTE effects on lower birthweight among boys (Tayie and Powell, 2012), lower positive mood (Pickett et al., 2008), higher peak cortisol reactivity (Schuetze et al., 2008), lower attentional response (Schuetze et al., 2013), and lower delay of gratification at preschool age (Wiebe et al., 2015) compared to exposed girls. A few studies also reported stronger associations between PTE and behavior problems among boys compared to girls, although these results are not consistent and many studies did not examine the role of child sex as a moderator (see Coles et al., 2012; review). In contrast, few studies examined sex as

a moderator of cannabis exposure effects, with one exception indicating higher inattention and aggression among cannabis exposed girls but not boys (El Marroun et al., 2011) and no sex differences by 36 months of age (see Huizink, 2014, review). While inconsistent, this literature does suggest that there may be sex differences in the association between PTE/PTCE and infant/toddler outcomes.

The purpose of this study was to examine a conceptual model of the association between tobacco and co-occurring tobacco and cannabis exposure on toddler emotion regulation (at 24 months of child age) via autonomic regulation in infancy (9 months of child age) and to examine the role of continued postnatal exposure, maternal dysregulation, and maternal sensitivity as additional predictors of toddler emotion regulation (see Fig. 1). A related goal was to examine if the associations between prenatal or postnatal exposure and toddler emotion regulation was moderated by child sex. Given lack of consistent previous findings, we did not have any specific hypotheses regarding direction of effect.

2. Method

2.1. Participants

All pregnant women presenting for prenatal care at a large local hospital were screened for substance use and additional eligibility criteria at their first prenatal appointment. Initial eligibility criteria included the following: < 20 weeks gestation, single births, maternal age of 18 years or older, no illicit drug use other than cannabis, no heavy alcohol use (women drank < 4 drinks per occasion and did not average > 1 drink a day), and were able to complete the self-report screening form in English. All recruited women were in their first trimester of pregnancy. The study was initially designed to examine effects of maternal tobacco use on developmental mechanisms and outcomes. Thus, tobacco users were oversampled based on this initial screener so that the closest eligible non-smoking woman (matched on. maternal age and highest educational attainment) was recruited for every two smoking women. The rationale for oversampling was to allow for a full range of light to heavy smokers, and the possibility for greater attrition among tobacco smokers.

The initial sample consisted of 258 mother-infant dyads (181 tobacco smokers, and 77 non-smokers). Of these 11 women were dropped from analyses for the following reasons: one dyad was dropped because infant meconium was positive for methamphetamine, two were dropped because of hydrocephaly, two were dropped because they were subsequently diagnosed with autism, one was dropped because other measures of substance use (see below) indicated > 4 drinks per day in pregnancy, and one was dropped because maternal cognitive functioning was low. Four additional dyads were excluded because they were initially assigned to the control group but reported using moderate levels of cannabis during pregnancy, resulting in a final sample size of 247 mother-infant dyads. Among the tobacco users, 97 mothers also used cannabis (51 infants were boys) and 81 only used tobacco (47 were boys). There were 69 mother-infant dyads in the non-substance using group (33 were boys).

At the first prenatal assessment (at the end of the 1st trimester), mothers ranged in age from 18 to 39 (M = 24.09, SD = 5.00). Mothers were racially diverse, with 51% African-American, 31% Caucasian, 19% Hispanic (8% Hispanic White, 11% Hispanic Black, and 81% only identifying race/ethnicity as Hispanic), and 8% other or mixed race, 45% were married or living with their partner, 33% were in a relationship but not living with their partner, 21% were single, and 1% were divorced. Close to a third of the women (29.5%) had not completed high school, 29.5% completed high school, 28% completed some college, 9% had a vocational, technical or associates degree, and only 4% had a bachelor's degree. Majority of mothers received Women, Infants, and Children (WIC) program (64.8%), 14.6% received Temporary Assistance for Needy Families (TANF), and 54.3% received food stamps. Thus, the mothers were diverse, mostly young, lower income, with relatively low levels of education.

2.2. Procedures and instruments

Women were assessed once toward the end of each trimester after informed written consent, obtained at the first prenatal assessment. Postnatal assessments were conducted at 2, 9, 16, and 24 months infant age, with the first three assessments at infant age corrected for prematurity. Mothers were paid for each assessment and infants received toys. Substance use data were protected by a Federal Certificate of Confidentiality from the National Institutes of Health.

2.2.1. Prenatal substance use

All maternal substance use data were measured through multiple methods that included self-reports and biological assays. Mothers were administered the Timeline Follow-Back Interview (TLFB; Sobell and Sobell, 1992) toward the end of each trimester. The TLFB yielded daily data regarding maternal substance use. Mothers were provided a calendar on which they identified approximate data of conception as well as salient events in each month (e.g., holidays, birthdays, parties, sports events, anniversaries, funerals, vacations, etc.) as anchor points to aid recall. The TLFB is a reliable and valid method of obtaining data on substance use patterns, including tobacco and cannabis (Robinson et al., 2014), has good test-retest reliability, and is highly correlated with other intensive self-report measures (Brown et al., 1998). The TLFB yielded data on the average number of cigarettes and joints smoked per day across the entire pregnancy, as well as the average number of alcoholic drinks per day across pregnancy. Several women in the tobacco group smoked cannabis in the form of blunts (rolled in tobacco leaf wrapper). They were asked to report the approximate number of joints they could have rolled with the amount of cannabis in blunts, in order to have a unified measure of dose of cannabis exposure. Given exclusion criteria regarding alcohol, the average drinks per day across pregnancy variable was bimodal in distribution, with 45% (n = 112) of mothers reporting no alcohol use in pregnancy, and the remainder reporting low use (see Table 1). Thus, this variable was dummy coded into 0 = no pregnancy alcohol use and 1 = some pregnancy alcohol use for model testing.

In addition to maternal self-reports, maternal oral fluid samples were analyzed by the US Drug Testing Laboratory (Des Plaines, IL) for cotinine, the primary nicotine biomarker, and for THC, the primary psychoactive component of cannabis. Cotinine assays were conducted with enzyme-linked immunosorbent assay (ELISA) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) at 10 ng/mL cutoff, and ranged from 0 to 569 ng/mL. Assays for THC were conducted with immunoassay screening (4.0 µg/L cutoff) and GC–MS confirmation (4.0 µg/L cutoff). Infant meconium samples were collected across several days after delivery in one collection bottle, and were assayed with a validated LC–MSMS method (Gray et al., 2010a) at 2.5 ng/g nicotine, 1 ng/g cotinine, and 5 ng/g OHCOT, and with a validated 2-dimensional GC–MS analytical method for THC, 11-hydroxy-THC; 8,11-dihydroxy-THC; 11-nor-9-carboxy-THC (THCCOOH), and cannabinol (Gray et al., 2010b). Limits of quantification for cannabinoid meconium assays were 10 ng/g for all analytes, except 11-hydroxy-THC at 15 ng/g. Mothers were assigned to the PTE group if they self-reported smoking during pregnancy on the screener or the TLFB, if oral fluid samples were cotinine positive, or if infant meconium was positive for cotinine, nicotine, or trans-3′ hydroxycotinine (OHCOT). Mothers were assigned to the PTCE group if they self-reported cannabis use during pregnancy, if infant meconium was positive for cannabinoids, or if oral fluid was positive for Δ9-tetrahydrocannabinol (THC) in any of the 3 trimesters.

2.2.2. Postnatal substance use

Toddler postnatal tobacco exposure was assessed during the 2, 9, 16 and 24 month laboratory visits using infant oral fluid samples assayed for cotinine. Infant and toddler oral fluid samples were collected by

Table 1
Group differences.

	Non-smoking	Tobacco only	Tobacco & cannabis	F/χ^2	Partial η^2
	M/% (SD) *n* = 69	*M*/% (SD) *n* = 81	*M*/% (SD) *n* = 97		
Maternal					
Age	24.45 (5.02)	24.90 (5.19)	23.81 (4.77)	0.78	0.01
Years of education	12.55 (1.90)	12.25 (1.84)	12.23 (1.90)	0.69	0.01
Occupation	2.13 (1.63)	2.24 (1.80)	1.95 (1.43)	0.72	0.01
Parity	1.51 (1.61)	1.86 (1.61)	1.46 (1.68)	0.88	0.01
Race (% Minority)	82.6%	58.2%	68.0%	$\chi^2 = 10.30^{**}$	
Married/Cohabiting	53.6%	49.4%	37.1%	$\chi^2 = 5.21$	
TANF	13.8%	13.8%	15.5%	$\chi^2 = 0.22$	
Medicaid	65.2%	64.5%	69.1%	$\chi^2 = 0.42$	
Food stamps	52.2%	52.5%	56.7%	$\chi^2 = 0.45$	
Partner smoking	40.5%	70.7%	91.7%	$\chi^2 = 21.87^{***}$	
Cumulative demo risk	0.51 (0.25)	0.49 (0.25)	0.51 (0.25)	1.60	0.01
Prenatal exposure					
# Joints/day	$.00^a$ (0.02)	$.00^a$ (.00)	$.57^b$ (0.86)	33.05^{***}	0.21
# Cigarettes/day	$.00^a$ (.00)	4.28^b (4.61)	5.56^c (4.63)	42.27^{***}	0.26
# Standard drinks/day	$.02^a$ (0.04)	0.05 (0.10)	$.10^b$ (0.24)	5.79^{**}	0.05
Postnatal exposure					
# Joints/day 2–24	$.01^a$ (0.04)	$.04^a$ (0.19)	$.70^b$ (1.20)	22.87^{***}	0.16
# Cigs/day 2–24	$.14^a$ (0.73)	4.89^b (4.39)	6.81^c (5.22)	52.49^{***}	0.30
Infant cotinine 2–24	1.75^a (1.43)	4.92^b (5.12)	7.65^b (8.01)	20.07^{***}	0.14
# Drinks/day 2–24	0.05 (0.15)	0.17 (0.33)	0.26 (0.56)	5.46^{**}	0.04
Maternal sensitivity: I	6.04^a (1.24)	6.09^a (1.36)	5.54^b (1.70)	3.21^{*}	0.03
Maternal sensitivity: T	11.35 (3.57)	11.55 (2.76)	11.58 (3.09)	0.91	0.001
Maternal dysregulation	11.99^a (11.28)	17.16^b (11.67)	13.34 10.57)	3.83^{*}	0.04
Maternal psyc. risk	0.31^a (0.12)	0.39^b (0.13)	0.37^b (0.12)	6.77^{**}	0.06
Infant baseline RSA	0.02 (0.01)	0.02 (0.01)	0.02 (0.02)	0.67	0.004
Infant RSA change	$-.003^a$ (0.01)	0 (0.01)	$.01^b$ (0.03)	3.43^{*}	0.04
Toddler regulation	18.32 (5.42)	18.04 (5.53)	16.95 (5.47)	0.30	0.01

Note. TANF: Temporary Assistance to Needy Families; Demo: Demographic; I: infancy; T: toddler period; RSA: respiratory sinus arrhythmia, Psyc: Psychological. The cell sizes for maternal sensitivity in infancy were 62, 64, and 83; for maternal sensitivity in toddler period were 57, 56, and 81; for maternal dysregulation were 59, 67, and 85; RSA variables were 57, 57, and 78 for control, tobacco only, and tobacco + cannabis groups respectively. Means with different superscripts were significantly different from each other.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

placing two eye spears (BD Opthalmology "Visispears" [product #581089], marketed by Salimetrics as "Sorbettes" [product #5029]) into the mouth of each child at each laboratory visit. Once collected, samples were placed in a storage vial and immediately moved to the −80 °C freezer to await shipment to the Center for Interdisciplinary Salivary Bioscience at Johns Hopkins University for assay. Oral fluid cotinine concentrations are highly correlated to those in blood (Jarvis et al., 2003) and, thus, are an accurate, yet noninvasive, way of measuring postnatal exposure in children. An additional benefit of oral fluid testing is that it quantifies exposure to cigarette smoke from all possible sources, including other household smokers. Total postnatal exposure was calculated by averaging child cotinine from 2 to 24 months child age in order to obtain a measure indicated cumulative child exposure across time. Postnatal cannabis and alcohol exposure was measured using maternal reports on the TLFB at the 2, 9, 16, and 24 month appointment. As with prenatal exposure, the TLFB yielded data on the average number of joints smoked per day during each assessment period (blunts were covered to number of joints that could be rolled with that amount of tobacco given the focus on dose-response associations) and average number of drinks per day. These were significantly correlated across time (Pearson correlation coefficients ranging from 0.31 to 0.77 for cannabis and 0.20 to 0.43 for alcohol, with higher correlations at adjacent time points, $p < .01$), and the four time points were averaged to create two composite variables reflecting postnatal cannabis and alcohol exposure.

2.2.3. Cumulative demographic risk

The cumulative demographic risk score was comprised of 4 factors: maternal race, maternal education, maternal occupation, and maternal partner status. For all items, a higher score was indicative of greater risk. Risk score for maternal race was coded as positive (1) if mothers indicated that they belonged to any minority race, with 69% meeting this criterion. The risk variable for maternal education was coded as positive (1) if the mother had not received a high school diploma or equivalent, and 29.1% met this criterion. Maternal occupation was coded using the Hollingshead scale ($M = 2.06$, $SD = 1.6$, *Range* = 1–8), with higher scores indicating higher occupation. This score was then divided by the maximum value of 9 in order to create a proportional risk score. This was then recoded so that higher numbers indicated greater risk (lower occupational status). The risk variable for partner status was coded as positive (1) if the participant was not married or living with a partner, and 54.7% of the sample met this criteria. The final demographic cumulative risk variable was created by averaging the 4 items described above, with a possible maximum score of 1 ($M = 0.67$, $SD = 0.27$, *Range* = 0.07–0.96).

2.2.4. Respiratory sinus arrhythmia

The physiological assessment of infant reactivity and regulation was recorded at 9 months infant age during a 3-min baseline interval (watching a video) and a stress/frustration episode (2 min) by examiners blind to infant group status. Testing occurred while infants were seated in a high chair, with their mothers seated directly to their left. Mothers were instructed not to interact with their infants during these procedures. Recording of the physiological data began once the infant was observed to be in a stable, quiet, alert state, which was induced by having the infant watch a 3-min segment of a neutral "Baby

Einstein" videotape (see Calkins, 1997). Immediately following the video, examiners began the gentle arm restraint paradigm that is a widely used, well-validated measure of anger/frustration used to assess infant regulation and reactivity (Goldsmith et al., 1999; Stifter and Braungart, 1995). During this episode, the child was first presented and encouraged to play with an attractive toy for 30 s. The experimenter then stood behind the child, placed her hands on the child's forearms, moved them to the child's sides, and held them there for 30 s, while maintaining a neutral expression (first trial). After the first trial, the infant was allowed to play with the toy for another 30 s followed by a second arm restraint (trial 2). The infant was again allowed to play with the toy after the 30 s of arm restraint. The session was stopped at the caregiver's request or if the child reached a maximum distress code, defined as the child reaching the highest intensity of negative affect of a full cry. This occurred for six infants (1 non-exposed and 5 cigarette-exposed). A five-channel Bioamp (James Long Company, Caroga Lake, NY) recorded respiration and electrocardiograph (ECG) data. Disposable electrodes were triangulated on the infant's chest. A respiration bellows was placed at the bottom of the sternum (zyphoid process) to measure inspiration and expiration.

IBI Analysis software (James Long Company, Caroga Lake, NY) was used to process the HR data and calculate RSA. HR samples, which were collected every 10 millisecond (ms), were used to calculate mean HR. A level detector was triggered at the peak of each R-wave. The interval between sequential R-waves was calculated to the nearest ms. Data files of R-wave intervals were later manually edited to remove incorrect detection of the R-wave or movement artifacts by a blind assessor. This occurred in 9 cases. In 8 of these cases, manual editing occurred for < 1% of data points. For one case, approximately 2% of data points required manual editing. The software computes RSA using respiration and interbeat interval data, as suggested by Grossman (1983). The difference between maximum interbeat interval during expiration and the minimum interbeat interval during inspiration was calculated. The difference, measured in seconds, is considered to be a measure of RSA, and is measured twice for each respiration cycle (once for each inspiration and once for each expiration). The time for inspirations and expirations is assigned as the midpoint for each. The time for each arrhythmia sample is assigned as the midpoint between inspiration and expiration times. The software synchronizes with respiration and is, thus, relatively insensitive to arrhythmia due to tonic shifts in heart rate, thermoregulation, and baroreceptor. Average RSA was calculated for the 3-min baseline and for each of the two trials of the arm restraint paradigm. The RSA change score, from the baseline to the second trial of arm restraint (when stress was highest) was calculated to assess autonomic regulation. A negative score indicates a decrease in RSA and is reflective of more optimal parasympathetic regulation.

2.2.5. Maternal dysregulation in infancy

Maternal dysregulation was measured using the Dysexecutive Functioning Questionnaire (DEX; Barker et al., 2011; Bodenburg and Dopslaff, 2008; Wilson et al., 1996) during the 9 month assessment. The DEX consists of 20 items that measure cognitive, behavioral, and emotional regulatory problems, with higher scores indicating higher dysregulation. Mothers reported the degree to which the items were relevant to their own thoughts, behaviors, and emotions on a 5-point Likert scale ranging from 0 (never) to 4 (very often), with higher scores indicating higher dysregulation. Internal consistency of the scale in the current sample was excellent, Cronbach's $\alpha = 0.90$.

2.2.6. Maternal psychological risk

Maternal psychological risk scores at 9 months were comprised of 4 factors: maternal depression, stress, anger, and hostility. For all items, a higher score was indicative of greater risk. Correlations between the 4 risk factors ranged from $r = 0.39$ to $r = 0.68$ and were all significant at $p < .001$. Mother's reported on their depressive symptoms using the Beck Depression Inventory (Beck et al., 1996) at the 9 month postnatal appointment. A proportion score was created by dividing each participant's score by the maximum possible score on the scale (63). Reliability of the scale was good, Cronbach's $\alpha = 0.90$. The same approach was used for maternal stress, reported at the 9 month postnatal appointment using the Perceived Stress Scale (Cohen et al., 1983). Proportion scores were again created by dividing each score by the maximum possible score on the scale (56), and reliability of this scale was also good, $\alpha = 0.83$. Maternal anger and hostility were assessed using the Buss Perry Questionnaire (Buss and Perry, 1992), and each subscale score was divided by subscale maximum scores (35) to create a proportion. Reliabilities were $\alpha = 0.73$ for maternal anger and $\alpha = 0.80$ for maternal hostility. The final maternal psychological risk variable was created by averaging the 4 items described above, with a possible maximum score of 1 ($M = 0.35$, $SD = 0.13$, *Range* = 0.03–0.75).

2.2.7. Maternal sensitivity in infancy

Maternal sensitivity during infancy was assessed during a free play interaction in the laboratory at 9 months of infant age. Mothers were asked to spend time with their infant as they normally would at home in a room that was furnished as a living room with a play mat and toys on the floor. Mother-infant interactions were videotaped and coded using the Ainsworth sensitivity vs. insensitivity and cooperation vs. interference scales (Ainsworth et al., 1974). The two scales were highly correlated ($r = 0.73$) and were averaged to reflect a composite maternal sensitivity measure. Two coders blind to group status rated maternal behavior. After training, inter-rater reliability was conducted on a random selection of 11% of the interactions ($n = 28$). The intra-class correlation coefficient for the association between the two coders was 0.90 for maternal sensitivity at 9 months.

2.2.8. Maternal sensitivity in the toddler period

Maternal sensitivity during the toddler period was assessed in the laboratory during a 5-min emotion regulation paradigm (Newby and Campbell, 1999). Mother–child dyads were left in the room with no toys or activities to interest the child. Mothers were asked to sit at a table and complete questionnaires. This situation is generally stressful for both mothers and reflective of naturalistic situations where they may have competing demands on their attention (Newby and Campbell, 1999). Maternal behavior was coded with a collection of 4-point scales across each one min episode and scores averaged across the five episodes following guidelines by Newby and Campbell (1999). The composite scale for maternal sensitivity was derived by taking the sum of four items (positive responsiveness, balance between task demand and child demand, maternal warmth, and encouragement of self-regulation) averaged across the five min, and had adequate internal consistency, Cronbach's $\alpha = 0.74$. Two coders blind to group status rated maternal behavior. After training, inter-rater reliability was conducted on a random selection of 10% of the interactions ($n = 24$). The intra-class correlation coefficient for the association between the two coders was 0.82 for maternal sensitivity at 24 months.

2.2.9. Toddler emotion regulation

Toddler emotion regulation was assessed in the laboratory during the 5-min emotion regulation paradigm (Newby and Campbell, 1999) as described above. Toddler behavior was coded for one min episodes and averaged across the 5 min following guidelines by Newby and Campbell (1999). The composite scale for toddler emotion regulation was derived by taking the sum of 10 items (low demandingness, high positive affect, low negative affect, positive responsiveness to mother, low negative responsiveness to mother, and high self-reliance), and had high internal consistency, Cronbach's $\alpha = 0.90$. Two coders blind to group status rated toddler behavior. After training, inter-rater reliability was conducted on a random selection of 10% of the interactions ($n = 24$). The intra-class correlation coefficient for the association between the two coders was 0.94 for toddler emotion regulation at 24 months.

2.3. Analytic strategy

We first examined associations among demographic risk, prenatal tobacco and cannabis exposure groups, continued postnatal exposure to both substances, infant RSA baseline and change, maternal sensitivity in infancy and toddler period, and toddler emotion regulation using Pearson correlations or ANOVAs as appropriate. For descriptive purposes, we also examined group differences in prenatal substance exposure variables that included the dose response variables of the average number of cigarettes and joints per day as well as results stratified by child sex.

Then structural equations modeling (SEM) tested the hypothesized model with infant RSA baseline and change, and maternal sensitivity in infancy as mediating variables between prenatal substance exposure groups and toddler emotion regulation and maternal sensitivity. Exploratory analyses examining if these hypothesized paths were different for boys vs. girls were examined with multiple group analyses. Nested χ^2 difference tests evaluated equality constraints of path coefficients for boys and girls. All SEM analyses were conducted in AMOS (Version 23.0; Arbuckle, 2014).

2.3.1. Missing data

As expected in any longitudinal study, there were incomplete data for some participants at one or more of the three assessment points included in this study. Of the 247 mother-infant dyads who completed the pregnancy and 2-month assessments, 192 participants had 9 month RSA data, 210 participants had maternal warmth data at 9 months, 211 participants had data on maternal dysregulation, and 194 participants had emotion regulation data at 24 months (see Table 1 note for specific sample sizes by group status), and 162 (66%) had complete data at all 3 time points. There were no significant differences between families with complete vs. missing data on any variable included in this study and demographics at any age and missing data patterns were unrelated to group status. Full information maximum likelihood procedures handled missing data in SEM.

3. Results

3.1. Descriptive data and group differences

Descriptive data regarding prenatal cigarette and cannabis use across the three groups and group differences in demographic variables are presented in Table 1, and group differences stratified by child sex are presented in Table 2. There were a higher percentage of minority women in the control group compared to both exposure groups. As would be expected, mothers in the exposure groups had more smoking partners and had greater tobacco intake, and mothers in the co-exposure group used more cannabis and alcohol, compared to those in the control group. The amount of cotinine in infant/toddler oral fluid (composite of 2 to 24 month cotinine levels) was higher in the exposure groups compared to the control group. There were no group differences on maternal sensitivity, infant baseline RSA or toddler emotion regulation. However, mothers in the PTE group had significantly higher dysregulation compared to mothers in the control group. In addition, infants exposed to both cannabis and tobacco exhibited a maladaptive increase in RSA in response to increasing stress compared to infants in the control group who exhibited an adaptive decrease in RSA (see Table 1).

Correlations among variables included in testing the hypothesized model indicated that higher demographic risk was associated with lower maternal sensitivity in infancy and the toddler period, and with a decrease in RSA in response to stress (see Table 3). Higher maternal dysregulation was associated with lower maternal sensitivity in infancy. There was modest stability in maternal sensitivity from infancy to toddler period. Decrease in RSA in response to stress and lower oral fluid cotinine across the infant/toddler period was associated with higher toddler emotion regulation. Higher maternal sensitivity in the toddler period was associated with lower toddler emotion regulation. Although not depicted in Table 3, maternal alcohol use (average number of standard drinks/day in pregnancy and across the postnatal time points) were not significantly associated with any of the variables in the model with one exception. Maternal postnatal alcohol use was associated with higher maternal dysregulation ($r = 0.20$, $p = .004$).

3.2. Model testing

Next, we tested the hypothesized model with the dummy coded prenatal group status variables (tobacco only vs. not and both tobacco and cannabis vs. not), prenatal alcohol use (0 = no use), and the cumulative demographic risk as exogenous variables in the model. We included direct paths from these variables to maternal sensitivity during mother-infant interactions at 9 months, infant baseline RSA and RSA change in response to stress, maternal dysregulation and psychopathology risk, and the three composite variables for postnatal tobacco,

Table 2
Group differences in endogenous variables stratified by child sex.

	Non-smoking	Tobacco only	Tobacco & cannabis	F/χ^2	Partial η^2
	M/% (SD)	*M*/% (SD)	*M*/% (SD)		
Girls					
Maternal sensitivity: I	6.09 (1.33)	6.02 (1.55)	5.52 (1.75)	1.49	0.03
Maternal sensitivity: T	12.22 (3.36)	11.90 (3.04)	11.97 (3.02)	0.91	0.001
Maternal dysregulation	13.52 (11.42)	18.19 (11.59)	14.88 (10.57)	1.31	0.03
Maternal psyc. risk	0.32 (0.13)	0.38 (0.13)	0.38 (0.12)	2.51	0.05
Infant baseline RSA	0.02 (0.01)	0.02 (0.01)	0.02 (0.02)	0.12	0.003
Infant RSA change	−0.004 (0.01)	0 (0.01)	0.0 (0.02)	1.14	0.03
Toddler regulation	17.52 (5.11)	17.95 (5.77)	17.29 (5.05)	0.11	0.00
Boys					
Maternal sensitivity: I	5.98 (1.58)	6.14 (1.24)	5.57 (1.66)	1.73	0.03
Maternal sensitivity: T	10.31 (3.58)	11.36 (2.61)	11.15 (3.15)	0.95	0.02
Maternal dysregulation	10.29^{a} (10.87)	16.51^{b} (11.82)	12.35 (10.36)	3.31*	0.06
Maternal psyc. risk	0.31^{a} (0.13)	0.40^{b} (0.14)	0.36 (0.11)	4.55*	0.08
Infant baseline RSA	0.016 (0.01)	0.018 (0.01)	0.019 (0.01)	0.58	0.01
Infant RSA change	−0.003 (0.006)	0 (0.01)	0.01 (0.03)	3.20*	0.06
Toddler regulation	19.26 (5.71)**	18.08 (5.48)	16.59 (5.87)	1.79	0.04

Means with different superscripts were significantly different from each other. I: infancy; T: toddler period; RSA: respiratory sinus arrhythmia, Psyc = psychological.
* $p < .05$.
** $p < .01$.

Table 3
Correlations among variables.

Variables	1	2	3	4	5	6	7	8	9	10	11
1. Pregnancy alcohol use											
2. Demographic risk	−0.11										
3. Baseline RSA	0.11	0.01									
4. RSA change	0.07	**−0.18**	−0.01								
5. Maternal sensitivity: I	**0.14**	**−0.23**	−0.07	0.01							
6. Toddler regulation	−0.08	0.02	−0.09	**−0.18**	0.09						
7. Maternal sensitivity: T	0.00	**−0.25**	−0.04	−0.01	**0.23**	0.01					
8. Postnatal infant cotinine	0.08	0.00	0.03	−0.02	−0.05	−0.02	0.01				
9. Postnatal joints/day	**0.17**	0.06	−0.02	**0.16**	**−0.27**	−0.08	−0.02	0.12			
10. Postnatal drinks/day	**0.21**	0.08	−0.09	−0.02	−0.03	−0.03	−0.08	0.08	0.11		
11. Maternal psychological risk score	0.10	−0.10	−0.08	−0.01	−0.07	−0.02	−0.05	0.03	0.08	**0.28**	
12. Maternal dysregulation	0.08	−0.11	−0.01	0.00	−0.12	−0.05	−0.10	0.01	0.08	**0.20**	**0.72**

Bolded numbers are significant at $p < .05$. Maternal psychological functioning risk score was a risk composite of maternal depression, anger/hostility/aggression measure, and perceived stress score. I: infancy; T: toddler period; RSA: respiratory sinus arrhythmia.

cannabis, and alcohol exposure across time. The model also included direct paths from these variables to toddler emotion regulation and maternal sensitivity during the no toy paradigm. Finally, we included within time causal paths from maternal sensitivity in infancy to infant baseline and change RSA, maternal dysregulation and psychological risk to maternal sensitivity, covariation between maternal psychological risk and dysregulation, and the covariance between the within time residuals for the two RSA variables (see Fig. 1).

This hypothesized model fit the data adequately, $\chi^2(18) = 32.09$, $p = 0.02$; CFI = 0.97; and RMSEA = 0.06 with 90% CI 0.02–0.09. However, given the significant bivariate association between demographic risk and maternal sensitivity in the toddler period, we added a direct path from prenatal demographic risk to maternal sensitivity. This resulted in a significant improvement in model fit, $\Delta\ \chi^2(1) = 10.24$, $p < .01$. The final model with this direct path included had the following fit indices, $\chi^2(17) = 21.85$, $p = 0.19$; CFI = 0.99; and RMSEA = 0.03 with 90% CI 0.00–0.07. As shown in Fig. 2, prenatal exposure to both tobacco and cannabis was associated with a maladaptive increase in RSA in response to stress during infancy, which in turn, was predictive of lower toddler emotion regulation. Exposure to tobacco only and co-exposure to both substances were associated with higher postnatal infant/toddler cotinine concentrations, which was associated with lower toddler emotion regulation. Maternal use of both tobacco and cannabis in pregnancy was also associated with lower maternal sensitivity in infancy and to higher maternal psychological risk. Maternal use of tobacco only was associated with higher maternal dysregulation. There was modest stability in maternal sensitivity from infancy to toddler period, and higher maternal sensitivity in the toddler period was associated with higher toddler emotion regulation. Cumulative demographic risk was associated with lower maternal sensitivity in infancy and in the toddler period, and to a decrease in RSA in response to stress. This model accounted for 20% of the variance in toddler emotion regulation.

The indirect effect from PTE to toddler emotion regulation was significant using bias corrected bootstrapped standard errors, B = −0.57 (95% CI: −1.44, −0.99), as was the indirect effect from PTCE to toddler emotion regulation, B = −1.76 (95% CI: −2.9, −0.06).

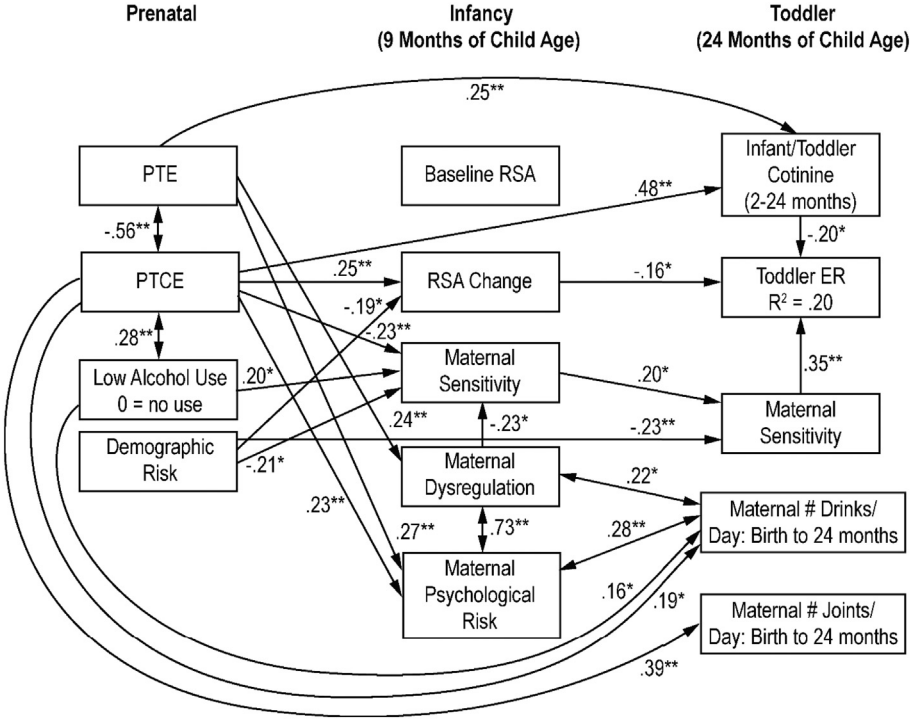

Fig. 2. Final estimated model. Only the significant paths are depicted in the model. The model also included the within time covariances among residuals. PTE: dummy coded tobacco exposure vs. not, 0 = not tobacco exposed; PTCE: dummy coded both tobacco and cannabis exposure vs. not, 0 = not exposed to both; Prenatal Alcohol Exposure: 0 = no use; RSA: Respiratory sinus arrhythmia; ER: Emotion regulation.

3.3. Child sex as moderator

We conducted multiple group analyses to examine if the paths in the hypothesized model were moderated by child sex. An unconditional model with the path coefficients free to vary for both boys and girls was estimated first. We then constrained the path from co-exposure to tobacco and cannabis to infant RSA change and the path from infant RSA change to toddler emotion regulation. The change in chi-square was non-significant indicating that boys and girls did not vary significantly in this association. Next, we constrained the path from postnatal infant/toddler cotinine to toddler emotion regulation. There was a significant difference in this path between boys and girls, $\chi^2(1) = 5.09, p < .05$. Specifically, higher infant/toddler cotinine was associated with lower toddler emotion regulation for boys ($\beta = -0.34, p < .001$), but not for girls ($\beta = 0.04$, $p = .69$). There were no other significant differences between boys and girls.

4. Discussion

There was no direct association between prenatal tobacco or co-exposure with cannabis in toddler emotion regulation. However, results indicated significant indirect associations between exposure and toddler regulation. Co-exposure to both tobacco and cannabis was associated with less adaptive RSA change in response to stress in infancy, which in turn was predictive of low toddler regulation. In addition, PTE was associated with maternal dysregulation, which in turn was predictive of lower maternal sensitivity in infancy. There was modest stability in maternal sensitivity from infancy to toddler period, and higher maternal sensitivity during the emotion regulation task was associated with higher toddler regulation. Of note, continued postnatal infant oral fluid cotinine was associated with lower toddler regulation, but continued postnatal maternal cannabis use did not account for unique variance in toddler regulation.

We were unable to find any previous studies linking dual exposure to both tobacco and cannabis and autonomic regulation in infancy, although a few studies have indicated significant associations between tobacco exposure and autonomic regulation among neonates and infants. For instance, tobacco exposed newborns had lower heart rate variability in quiet sleep compared to controls (Fifer et al., 2009), but this study only included self-reports of substance use and only include alcohol among other substances. Similarly, in a small sample of infants ranging from 6 to 16 weeks, Franco and colleagues (Franco et al., 2000) noted significant differences between infants of smokers vs. non-smokers in autonomic regulation during REM sleep, with infants of smokers displaying lower long term parasympathetic tone during rest compared to infants of non-smokers, a non-adaptive response. Studies in later infancy reported similar disturbances in autonomic functioning, with lower baseline RSA during rest among tobacco exposed infants (Schuetze and Eiden, 2006; Schuetze and Zeskind, 2001; Zeskind and Gingras, 2006). In an earlier report of the current sample, we noted that there was significant RSA suppression in response to negative emotion among control infants, but not among tobacco exposed infants (Schuetze et al., 2013), but did not examine if these differences were more pronounced among infants exposed to cannabis as well. However, studies among cannabis using adults have noted that cannabis use is associated with higher heart rate variability compared to non-drug using control men (Schmid et al., 2010), cannabidiol reduces autonomic arousal and subjective anxiety (Fusar-Poli et al., 2009), and there is a temporal association between recreational cannabis use and serious adverse cardiovascular events (Singh et al., 2017). Our current results highlight the importance of examining co-exposure effects separate from tobacco effects, and suggest stronger effects on infant autonomic regulation among tobacco exposed infants who were also exposed to cannabis. However, given the sparse literature, these results need to be replicated in other samples of co-users.

Our results support and extend prior literature on the associations between RSA change in response to challenge and different aspects of emotion regulation in early childhood by examining this association among a diverse group of primarily low-income, substance-exposed infants/toddlers. In addition, while a number of studies noted associations between RSA suppression and aspects of emotion regulation (e.g., Cho et al., 2017), few used behavioral measures of emotion regulation in contexts that have some ecological validity, such as toddler emotion regulation when parents are busy or involved with other activities and there are few distractions present in the environment. Most prior studies examined associations between RSA suppression and parent reports of behavior problems (e.g., Calkins et al., 2007; Cho et al., 2017). While some studies indicated no main effects of RSA on behavior problems, but an interaction with sleep duration at preschool age (Cho et al., 2017), a number of studies reported greater RSA suppression being associated with fewer behavior problems at preschool age (Calkins et al., 2007; Calkins and Dedmon, 2000; Calkins and Keane, 2004; Porges et al., 1996). Future studies may well examine if the association with behavioral measures of emotion regulation are replicated in other samples as well, given the great diversity of emotion regulation assessments in developmental science (Adrian et al., 2011).

In addition to RSA suppression, the co-use of tobacco and cannabis was associated with lower maternal sensitivity in infancy, there was modest stability in maternal sensitivity across time, and lower maternal sensitivity in the context of the emotion regulation task at toddler age was significantly associated with lower toddler emotion regulation. Results are supportive of theoretical models of children's affect regulation as developing in the context of synchronous affective interactions with primary caregivers (Schore, 1994), the hallmark of high sensitivity. Results are also supportive of the larger literature on maternal sensitivity playing a critical role in development of child emotional and behavioral regulation (Feldman et al., 2011; Feldman et al., 1999; Kochanska et al., 2008), and extend those findings to a diverse sample of low-income, substance exposed children. There was a significant association between some prenatal alcohol use (some use vs. no use) and higher maternal sensitivity. This can only be interpreted in the context of a sample with low levels of maternal drinking during pregnancy, with most use occurring before pregnancy recognition, since this was an exclusion criteria. Given that most studies of prenatal alcohol use include moderate to heavy drinking women, it is not clear how to interpret these results based on the literature and results need to be replicated.

Surprisingly, mothers in the PTE group had higher dysregulation than mothers in the PTCE group, even though the co-using mothers had the highest cigarette smoking and more partners who were smokers. Given the lack of prior studies on maternal dysregulation and co-use of tobacco and cannabis, these results may be sample specific. Another possibility is that mothers in the co-use group used cannabis to self-medicate and reported lower dysregulation symptoms. Future studies with more objective measures of maternal regulation may be informative. Mothers in both exposure groups had higher psychological symptom risk scores that included depression and anger/hostility symptoms. Higher maternal psychological risk was not associated with maternal or toddler behaviors, but was associated with higher maternal dysregulation. Both maternal dysregulation and higher maternal psychological risk were associated with higher postnatal alcohol use.

Finally, continued postnatal tobacco exposure as assessed by infant oral fluid cotinine across the infant/toddler period was associated with lower toddler emotion regulation, and these results were significant for boys, but not girls. Few previous studies examined postnatal tobacco effects on children's emotion regulation in the context of prenatal exposure. However, these results are generally supportive of previous studies indicating associations between postnatal tobacco exposure and higher behavior problems at 3 years of child age, such as impulsivity and peer problems (Day et al., 2000). Results are also similar to those reported by Bada et al. (2011) indicating significant associations between postnatal tobacco exposure and higher externalizing behavior

problems, although neither of these studies reported sex differences.

The study adds to the larger literature on prenatal exposure effects, particularly the effects of polysubstance exposure, given the large co-morbidity of tobacco and cannabis use during pregnancy. In addition, the results highlight the importance of considering indirect pathways to emotion regulation via biological responses to challenge, the importance of considering the role of maternal sensitivity when examining child outcomes, and of continued postnatal exposure and sex differences. An additional strength is the use of behavioral challenge measures for autonomic regulation and measurement of emotion regulation, and use of observational methods for measurement of maternal sensitivity. In addition to these strengths, the study also has some limitations. One major limitation was that the measure of emotion regulation, while based on observational methods, was limited in context to the laboratory task. Results would be stronger if similar patterns were reported for other laboratory and home contexts as well. A second limitation was that while we had objective measurements of postnatal tobacco exposure, we did not have similar measures for postnatal cannabis exposure. This is mainly because the study was not originally designed to examine the effects of co-use of tobacco and cannabis, but was designed to examine tobacco effects. Thus, findings regarding co-use should be viewed with caution and will need to be replicated. Future studies may include oral fluid assays for markers of tobacco and cannabis exposure. In spite of these limitations, this study adds to the sparse literature on co-occurring tobacco and cannabis exposure effects, sex differences in postnatal exposure effects, and associations between parent and child behaviors in a low-income, diverse sample of mothers and children.

Transparency document

The Transparency document associated with this article can be found, in online version.

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