11-2018

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HHS Public Access

Author manuscript

Neurotoxicol Teratol. Author manuscript; available in PMC 2019 November 01.

Published in final edited form as:

Neurotoxicol Teratol. 2018 ; 70: 28–39. doi:10.1016/j.ntt.2018.09.003.

Prenatal tobacco and marijuana co-use: Impact on newborn neurobehavior[1]

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Abstract

Tobacco and marijuana are some of the most common prenatal substance exposures worldwide. The social acceptability and political landscape of marijuana and its potency have changed dramatically in the last two decades leading to increased use by pregnant women. Despite evidence for increasing marijuana use and high rates of co-use of tobacco (TOB) and marijuana (MJ) during pregnancy, the impact of prenatal exposure to each substance is typically studied in isolation. We investigated the influence of co-exposure to TOB and MJ on infant neurobehavioral development over the first postnatal month. Participants were 111 mother-infant pairs from a low-income, diverse sample (Mean age=25±5; 54% minorities). TOB and MJ use were assessed by Timeline Followback interview with biochemical confirmation. Three groups were identified: (a) prenatal MJ+TOB, (b) prenatal TOB only, (c) controls. Newborn neurobehavior was assessed at seven time points over the first postnatal month using the NICU Network Neurobehavioral Scale. MJ+TOB-exposed infants showed decreased ability to selfsoothe (Self-regulation) and attend to stimuli (Attention), and increased need for examiner soothing (Handling) and low motor activity

[1]**Non-standard Abbreviations:** TOB - Tobacco - MJ - Marijuana - THC - Δ^9-tetrahydrocannabinol - BAM BAM - Behavior and Mood in Babies and Mothers study - NNNS - NICUNetwork Neurobehavioral Scale - ETS - environmental tobacco smoke - CO - carbon monoxide - SES - socioeconomic status r for publication

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(Lethargy) versus unexposed infants. Despite low levels of MJ use in MJ+TOB co-users, co-exposure was associated with nearly double the impact on infant self-soothing and need for examiner soothing versus TOB-exposure alone. Effects of MJ+TOB co-exposure appeared more pronounced for daughters than for sons. Although results are preliminary, they highlight additional risk from dual exposure to MJ+TOB vs. TOB exposure alone, particularly for daughters. Results also highlight the critical importance of investigating prenatal exposures in concert and the need for intervention efforts to address MJ co-use in pregnant TOB users.

Keywords

pregnancy; marijuana; tobacco; infant; behavior; NNNS

1. Introduction

Maternal tobacco (TOB) use during pregnancy remains an enormous public health problem in the US and worldwide. Despite large-scale public education campaigns, approximately one of every ten infants in the US is born exposed to tobacco (Curtin and Matthews, 2016; Drake et al., 2018; Tong et al., 2013; U.S. Department of Health and Human Services, 2014). Infants born to less educated, poor, and underserved mothers show disproportionately higher rates of TOB exposure (up to ~2 in 10 infants born exposed) (Tong et al., 2013). As documented in the 2014 Surgeon General's Report, prenatal exposure to cigarette smoking is considered causally linked to increased risk for infant morbidity and mortality including low birth weight, preterm birth, and sudden infant death syndrome (U.S. Department of Health and Human Services, 2014). In older children and adolescents, suggestive associations were shown between prenatal TOB exposure and altered neurobehavioral development, including disruptive behaviors/conduct disorder, attention deficits/attention deficit hyperactivity disorder, and smoking/nicotine dependence (Gaysina et al., 2013; Huang et al., 2018; Ruisch et al., 2018; Shenassa et al., 2015; U.S. Department of Health and Human Services, 2014).

Maternal marijuana use during pregnancy is also one of the most widespread prenatal drug insults in the US and the world (Center for Behavioral Health Statistics and Quality, 2015;World Health Organization, 2016). The social acceptability and political landscape of marijuana (MJ) have changed dramatically in the US in the last decade, accompanied by expanding legalization, decriminalization, and medicalization (Pew Research Center, 2015). Paralleling increased societal acceptance of MJ, rates of MJ use by pregnant women increased by sixty-two percent between 2002 and 2014, with current estimates of between 1 and 2 infants in every 20 born exposed, and increased rates in poor, young, and less-educated mothers (Brown et al., 2017; Ko et al., 2015; Substance Abuse and Mental Health Services, 2012; Substance Abuse and Mental Health Services Administration, 2014). Further, potency of Δ^9-tetrahydro-cannabinol (THC), the primary psychoactive ingredient in MJ, has increased 300% since 1995 (ElSohly et al., 2016; Mehmedic et al., 2010). The impact of prenatal MJ exposure on offspring development has received less research attention relative to tobacco. A recent meta-analysis found no effects of prenatal MJ exposure on preterm birth, but demonstrated a 77% increased risk for low birthweight in MJ-

exposed infants (Gunn et al., 2016); however, it was not possible to rule out effects on low birthweight due to other substance exposures. Longer-term studies have revealed some evidence for associations between prenatal MJ and impairments in attention and inhibitory control, impulsivity and hyperactivity, and increased risk of MJ use in child, adolescent, and young adult offspring (Day et al., 2006; Day et al., 2011; Day et al., 1994; Fried, 2002; Goldschmidt et al., 2012; Smith et al., 2006; Smith et al., 2016).

Approximately twenty to thirty percent of pregnant women who use TOB endorse MJ couse (Chabarria et al., 2016; Coleman-Cowger et al., 2017; Ko et al., 2015). Rates of TOB co-use among pregnant women who use MJ are even higher—approximately two-thirds to three fourths of pregnant MJ users endorse TOB co-use (Chabarria et al., 2016; Coleman-Cowger et al., 2017; El Marroun et al., 2008; Ko et al., 2015). In non-pregnant populations, MJ+TOB co-use was associated with worse health outcomes, including increased risk of both MJ and TOB use disorders, poorer MJ and TOB cessation outcomes, increased psychiatric conditions, and increased respiratory dysfunction (Agrawal et al., 2012; Peters et al., 2012; Peters et al., 2014; Rabin and George, 2015). In pregnant women, MJ+TOB co-use was associated with increased maternal (e.g., asthma and pre-eclampsia) and neonatal health risks (preterm birth, decreased birthweight and head circumference), increased risk for maternal psychiatric and alcohol use disorders, increases in other drug and poly-tobacco use, and difficulty with TOB cessation (Chabarria et al., 2016; Coleman-Cowger et al., 2017; Emery et al., 2016; Gray et al., 2010).

The impact of MJ+TOB on fetal development may be mediated by THC/cannabinoids and nicotine. Nicotine and THC freely cross the placenta and enter fetal circulation (Little and VanBeveren, 1996; Luck et al., 1985). In preclinical models, both prenatal nicotine and THC administration result in persistent alterations in neuronal development—nicotine via nicotinic acetylcholine receptors and disruption of brain cell replication and differentiation and THC via cannabinoid receptors and disruption of neuronal wiring (England et al., 2017a; Levin and Slotkin, 1998; Parsons and Hurd, 2015; Richardson et al., 2016). Both prenatal nicotine and THC also result in widespread disruption of neurotransmitter systems, including serotonergic, GABAergic, and dopaminergic systems (England et al., 2017a; Morena et al., 2016). Although to our knowledge, no preclinical models have investigated joint effects of prenatal nicotine and THC exposure, it is plausible that disruption of neuronal development via both nicotinic and endocannabinoid pathways may result in additive or synergistic effects of prenatal TOB+MJ on offspring neurobehavioral development.

Despite plausible neurobiological mechanisms and evidence for increased maternal and neonatal health risks from prenatal MJ+TOB exposure, few studies examined the impact of prenatal co-use on infant neurobehavioral development. Eiden et al. found that MJ+TOB coexposure was associated with less adaptive autonomic regulation at nine months, which was then associated with diminished emotion regulation at twenty-four months (Eiden et al., 2018). Schuetze et al. investigated prenatal MJ+TOB co-exposure effects on infant reactivity and regulation in the context of maternal and fetal mediators (maternal stress, anger, fetal growth) (Schuetze et al., 2018). No direct effects were found; however, prenatal MJ+TOB exposure was associated with altered fetal growth, which was then associated with altered

regulation and negative affect at 9 months. Finally, El Marroun et al. found effects of prenatal MJ exposure on offspring inattention and aggressive behavior in 18-month old infants, the majority of whom were also exposed to tobacco (El Marroun et al., 2011).

To our knowledge, no studies have explicitly examined the impact of prenatal MJ+TOB coexposure on newborn neurobehavioral development over the first postnatal month despite the importance of this period for (1) establishment of parent-infant attachment, (2) documenting the earliest unfolding developmental pathways leading to long-term child behavioral outcomes, and (3) investigating the impact of prenatal exposures prior to long-term exposure to second-hand tobacco/MJ smoke. Instead, effects of prenatal exposure to MJ or TOB on newborn neurodevelopment have typically been studied in isolation. Because the goal of many neurodevelopmental studies is to determine fetal neurotoxicity of a specific substance, typical studies include statistical control for co-exposures, but little systematic investigation of the potential unique or additive/synergistic impact of co-exposures on offspring outcomes (Lester and Lagasse, 2010).

Multiple prior studies investigated effects of prenatal TOB alone on newborn neurobehavior. In the early newborn period, TOB-exposed infants have shown increased irritability, excitability, and need for external soothing versus unexposed infants (Godding et al., 2004; Law et al., 2003; Mansi et al., 2007; Stroud et al., 2009a). In the later newborn period and in studies investigating neurobehavior across the first postnatal month, TOB-exposed infants showed decreased ability to self-soothe (self-regulation), increased need for external soothing (need for handling), decreased attention to stimuli (attention/orientation), and alterations in motor activity (including increased lethargy and arousal) (Espy et al., 2011; Stroud et al., 2016; Stroud et al., 2009b; Yolton et al., 2009). A much smaller number of studies examined links between prenatal MJ and newborn neurobehavior. In a middle-class, low risk sample, exposure to prenatal MJ was associated with poorer habituation to visual stimuli, increased arousal, excitability, and irritability, and decreased ability to self-soothe in the early newborn period (Fried, 1980; Fried and Makin, 1987). These effects were corroborated by studies designed to investigate other perinatal risk factors (prenatal cocaine exposure, adolescent pregnancy) (Coles et al., 1992; de Moraes Barros et al., 2006; Lester et al., 2002), but were not replicated in a high risk MJ-exposed sample (Richardson et al., 1989) or in a study of MJ exposure in Jamaican infants (Hayes et al., 1988).

Sex-specific effects of both prenatal TOB and prenatal MJ on offspring neurobehavior have been reported in a small number of studies. In older offspring, there is some evidence that prenatal TOB exposure exerts a more pronounced impact on offspring behavioral dysregulation and disruptive behavior disorders in sons, whereas the impact of prenatal TOB exposure on offspring tobacco and other drug use/disorders (including cannabis, cocaine), was more pronounced in daughters (Brennan et al., 2002; Coles et al., 2012; Fergusson et al., 1998; Kandel et al., 1994; Stroud et al., 2014b; Weissman et al., 1999). Further, prenatal MJ exposure led to increased infant inattention and aggression at 18 months in daughters but not sons (El Marroun et al., 2011). Sex-specific effects of both prenatal THC and prenatal nicotine exposure were also documented in animal models (Bonnin et al., 1996; Cross et al., 2017).

1.1. The Present Study

Despite evidence for overlapping alterations in newborn neurobehavior (including selfregulation, attention and motor activity) from TOB and MJ examined in isolation, to our knowledge, no studies investigated the impact of MJ+TOB co-use on newborn neurobehavior.

Thus, our first goal was to investigate the impact of prenatal MJ+TOB vs. TOB only versus no substance exposure on newborn self-regulation, need for external handling, attention, and lethargy over the first postnatal month. We hypothesized that MJ+TOB-exposed newborns would show altered ability to self-regulate, worse attention, and increased lethargy versus unexposed infants; we also explored the hypothesis that co-exposed infants would show worse neurobehavioral outcomes versus TOB-exposed infants. Given evidence of sex-specific effects of prenatal TOB and MJ in some prior studies of older offspring, our second goal was to explore the sex-specific impact of prenatal MJ+TOB vs. TOB only vs. no substance exposure on newborn neurobehavior.

2. Material and Methods

2.1. Study Design.

As shown in Figure 1, the Behavior and Mood in Babies and Mothers (BAM BAM) study was a prospective study of effects of maternal tobacco use in pregnancy on fetal and infant neurobehavior (Stroud et al., 2018; Stroud et al., 2014a; Stroud et al., 2016). Pregnant mothers were recruited from obstetrical offices, health centers, and community postings primarily during first and second trimester and were enrolled during late second or third trimester of pregnancy (*M*=31 weeks gestation, *SD*=2) between 2006 and 2010. Mothers completed between 2 and 4 (*M*=3, *SD*=1) interview sessions during second and third trimesters of pregnancy and at delivery (26–42 weeks gestation) depending on the timing of study enrollment and their availability for multiple assessments. Fifty percent completed 4 interview sessions; 45% completed 3 interviews, and 5% completed 2 interviews. Specifically, interview sessions took place at 31±2, 35±1, 36±1 weeks gestation and at 1±1 days post-delivery. Mean number of weeks between interview sessions was 3.5 weeks (*SD*=1.4). Meconium was collected following delivery to assess biomarkers for nicotine and other substances. Postnatal follow-up sessions included infant neurobehavioral examinations (NICU Network Neurobehavioral Scale; NNNS) and saliva samples to determine infant exposure to nicotine. Day 1 and Day 32 postnatal sessions also included maternal interview questions. Postnatal follow-up sessions were conducted up to 7 times over the first postnatal month (*Med*=7, *M*=6) at days 0 (*M*=8 hours), 1, 2, 4, 5, 11, and 32 (*SDs*=0.1, 0.3, 0.3, 0.6, 0.4, 2.3, and 3.1 days, respectively). All day 0 and 1 NNNS were conducted in the hospital, 56% of day 2—4 NNNS were conducted in the hospital; 99% of day 5—32 NNNS were conducted at participants' homes. Postnatal time points were selected to conduct a detailed examination of rapid neurodevelopment and potential nicotine withdrawal over the first 5 postnatal days, followed by longitudinal assessment over the remainder of the month (days 11 and 32).

2.2. Participants

Participants in the current study were a subsample from the BAM BAM Study (above). Maternal exclusion criteria included age <18 or >40, regular illicit drug use besides MJ (meconium confirmed), involvement with child protective services, and serious medical conditions (e.g., pre-eclampsia, severe obesity). Infants were healthy singletons born >36 weeks gestational age (GA) with no congenital anomalies or serious medical conditions. All procedures were reviewed and approved by local Institutional Review Boards.

One hundred forty-eight pregnant women ages 18–40 enrolled in the study. Of these, six were excluded for regular opiate or cocaine use, two for involvement with child protective services, five for maternal medical conditions, and six for delivery ≤ 36 weeks gestation. Ten infants who did not have neurobehavior data were excluded from analyses. Four participants who were missing maternal-report data regarding MJ use and four participants who used MJ, but not TOB, were excluded from analyses given our focus on MJ+TOB co-use. The final analytic sample (n=111) included 24 MJ+TOB users, 45 tobacco-only (TOB) users and 42 biochemically-verified controls. The MJ+TOB group included participants whose maternal report or biomarkers were positive for TOB and whose maternal report or biomarkers were positive for MJ. The TOB group included participants whose maternal report or biomarkers were positive for TOB, and whose maternal report and biomarkers were negative for MJ. The Control group included participants whose maternal report and biomarkers were negative for both TOB and MJ. Infant offspring included 51 daughters and 60 sons.

2.3. Procedures

2.3.1. Maternal Interviews.—During each interview, mothers completed the Timeline Followback (TLFB) interview (Robinson et al., 2014), a calendar/anchor-based assessment of tobacco, marijuana, and other substance use, adapted to assess use over pregnancy and three months prior to conception. Mothers also provided saliva samples for cotinine determination. Demographic characteristics, caffeine consumption, environmental tobacco smoke (ETS) exposure, health and pregnancy history and depression were also assessed. Finally, maternal weight and expired breath carbon monoxide were measured during third trimester. TLFB other substance use, caffeine, ETS, health and pregnancy history, depression, and weight were utilized to describe the sample and were also tested as potential confounders (*Section 2.4.*). Cotinine and carbon monoxide concentrations were utilized to examine differences between TOB and MJ+TOB groups.

2.3.2. Infant Neurobehavior over the First Postnatal Month.—The NICU Network Neurobehavioral Scale (NNNS) is an infant neurobehavioral assessment designed to reveal subtle differences in high-risk and substance-exposed infants (Lester et al., 2004; Tronick and Lester, 2013). The NNNS follows a standard but flexible (based on infant behavior) administration sequence that starts with pre-examination observation followed by neurologic and behavioral components (Lester et al., 2004; Tronick and Lester, 2013). The exam includes exposure to auditory, visual, social and non-social stimuli and lasts approximately 30 minutes (M=27 min; SD=5 min). NNNS subscales of focus for the present study include: Self-Regulation, Handling (need for external soothing of the infant to maintain a quiet alert state), Lethargy, and Attention. All NNNS were administered by

certified examiners who were blind to maternal substance exposure during pregnancy. Saliva samples collected at the time of the final NNNS examination (Day 32) were utilized to determine infant exposure to nicotine via environmental tobacco smoke (ETS) or breast milk. Time between last feeding and start of NNNS was recorded for use as an a priori covariate in multivariate models.

2.4. Bioassays

2.4.1. Saliva cotinine.—Saliva cotinine is a reliable biomarker for nicotine concentrations (Jarvis et al., 1987). Maternal and infant saliva samples were frozen until analysis by Salimetrics (www.Salimetrics.com) using highly-sensitive enzyme immunoassay. Intra and inter-assay coefficients of variation were 6.4% and 6.6%.

2.4.2. Breath Carbon Monoxide—Expired alveolar carbon monoxide (CO) is a biomarker of recent exposure to TOB or MJ combustion (Sandberg et al., 2011). CO concentrations in expired breath samples were measured in duplicate using the Bedfont Micro 4 Smokerlyzer (Bedfont® Scientific Ltd).

2.4.3. Meconium nicotine and cannabinoid biomarkers—Meconium was analyzed for nicotine markers (nicotine, cotinine, trans-3′hydroxycotinine), cannabinoid markers (Δ9-tetrahydrocannabinol (THC), 11-nor-9-carboxyTHC, cannabinol, 11-hydroxy-THC, di-OH-THC), opiates, cocaine, and amphetamines via EMIT screens, tandem liquid chromatography mass spectrometry or gas chromatography mass spectroscopy confirmation (Gray et al., 2009b; Moore et al., 1998). Samples from all participants were negative for cocaine, opiates, and amphetamines. Samples with nicotine or cannabinoid markers ≥10 ng/g were considered positive for nicotine and/or cannabinoids (Gray et al., 2009a).

2.5. Measurement of Potential Confounders

Multiple potential confounders of the association between prenatal TOB and MJ+TOB and infant outcomes were measured. *Maternal demographics*: age, race/ethnicity (% NonHispanic White), Hollingshead socioeconomic status (SES; low SES=Hollingshead ≥ 4); and *pregnancy history*: gravida, parity, were assessed by maternal report. *Maternal gestational medical conditions*, e.g., hypertension and diabetes were determined by maternal report and medical chart review. *Weight gain over pregnancy* was assessed by maternal report (prepregnancy) and study measurement (35±1 weeks). *Maternal depressive symptoms* were assessed by structured interview using the 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). The HDRS is the most commonly used measure of depression with demonstrated convergent validity, sensitivity/specificity, and test retest reliability (Hotopf et al., 1998;Mottram et al., 2000; Rehm and O'Hara, 1985; Reynolds and Kobak, 1995; Williams, 1988). *Maternal alcohol use* was assessed through TLFB interview (Robinson et al., 2014). *Maternal caffeine use and environmental tobacco smoke (ETS) exposure* were assessed by structured interview; *infant ETS exposure* was assessed by infant saliva cotinine. *Infant characteristics*: sex, delivery mode, GA at birth, small for GA (SGA; birth weight $<10^{th}$ percentile for GA), and Apgar were assessed by medical chart review. *Feeding method* (breast vs. bottle) was assessed by maternal report.

2.6. Statistical analysis

2.6.1. Testing of potential confounders—Each of the potential confounders described in *Section 2.4* was first tested individually in relation to exposure group (MJ +TOB, TOB, Control) using Kruskal-Wallis ANOVA as omnibus tests for continuous confounders, and by Chi-square and Fisher's exact tests (as appropriate) for discrete confounders (See Table 1). Potential confounders that showed significant differences across exposure groups (omnibus *p*s<.05) were further evaluated for associations with NNNS outcomes. Those showing significant associations with individual NNNS subscales (*p*s<.05) were included in the respective regression models (See below and Table 2). Specifically, feeding method (any breast-feeding) was a significant confounder for the NNNS Self-Regulation and Handling models; infant ETS and maternal depressive symptom exposure were significant confounders for the NNNS Lethargy and Attention models. All regression models also included time since feeding (log-transformed), an important determinant of infant neurobehavior, as an a priori covariate.

2.6.2. Longitudinal regression modeling.—Outcomes exhibiting significant skewness (NNNS Handling, NNNS Lethargy) were symmetrized via a logarithmic transformation. Effects of substance-exposure group on infant neurobehavior (NNNS Self-Regulation, Handling, Lethargy, Attention) over the first postnatal month were investigated using Generalized Least Squares regression modeling (Fitzmaurice et al., 2011). Generalized least squares regression modeling is an extension of repeated measures analysis of covariance which allows for: (a) heteroscedastic variances (i.e., unequal variance across NNNS visits), (b) correlations between NNNS visits for the same participant depending on their separation in time, (c) incorporation of time-varying covariates (e.g., time since feeding for each NNNS visit), and (d) intermittent missingness in NNNS visits over time. Specifically, although 111 infants contributed NNNS exams on at least one visit, NNNS exams on Days 0, 1, 2, 3, 5, 11, and 32 were missing for 14, 6, 10, 20, 23, 15, and 18 infants respectively (See Figure 1). Analyses for each outcome of interest were conducted using the *nlme* library of R 3.4.2 (https://cran.r-project.org) assuming group-specific variances and a continuous-time first-order autocorrelation. Residual standard deviations calculated in the Control group were used to convert group differences into effect sizes.

In the present analyses, substance exposure group was the between-subjects factor and infant age at the NNNS (log-transformed) was the within-subjects factor. Overall differences between the exposure groups in both outcome levels at the first NNNS exam (intercept) and with respect to infant age at NNNS exam over the first postnatal month (linear slope) were tested using multivariate Wald tests with 2 degrees of freedom. Significant omnibus association tests were followed by examination of pairwise contrasts (MJ+TOB vs. Control, TOB vs. Control, and MJ+TOB vs. TOB). Both omnibus and pairwise tests were adjusted for significant confounders. All associations were investigated in an overall model including all participants, and in identical models stratified by infant sex. Significant confounders from the overall sample were also utilized for sex-stratified models.

3. Results

3.1. Sample Characteristics

Descriptive statistics for the overall sample and stratified by substance-exposure group are presented in Table 1. The sample was primarily low socioeconomic status (55% ≤ high school education; 57% unemployed; 48% annual income <$20,000), and racially/ethnically diverse (18% African-American, 25% Hispanic, and 11% Multiracial/Other; 46% Non-Hispanic White). Infants ranged in age from 0–43 days. There were no significant differences in average cigarettes per day, or maternal cotinine or CO concentrations between TOB-only and MJ+TOB users. The 45 TOB-only users reported an average of 10±7, 6±6, and 5±6 cigarettes per day, and the 24 MJ+TOB users reported an average of 10±8, 6±6, and 4±4 cigarettes per day during first, second, and third trimesters. MJ+TOB users endorsed an average of 24 days of MJ use (*SD*=24) over pregnancy, with 24±24, 1±1, and 0.04±0.20 days of use during each trimester. Types of MJ use endorsed included: joints (33%), blunts (33%), multiple methods (13%; joints + blunts; bowls + joints) and unknown (8%), as well as three MJ+TOB users (13%) who denied MJ use on the TLFB but had positive meconium cannabinoids markers.

MJ+TOB and TOB-only mothers were more likely to be low SES, to be exposed to ETS, and showed greater depressive symptoms than Controls; their infants were less likely to be breast fed and showed increased cotinine vs. Controls. MJ+TOB users were more likely to use >1 drink/week than Controls; TOB-only users were more likely to use caffeine than Controls. Of maternal and infant characteristics which differed by exposure group, those that were also associated with individual NNNS subscales were included as confounders in the respective regression models below. These included: infant feeding method for NNNS Self-Regulation and Handling, and infant ETS and maternal depressive symptoms for NNNS Lethargy and Attention.

3.2. Overall impact of MJ+TOB and TOB-exposure on infant neurobehavior over the first postnatal month.

No differences among exposure groups emerged with respect to infant age effects over the first postnatal month for any NNNS subscale (linear slope x exposure group interaction *p*s>. 25). Therefore, interest centered upon group differences in outcome levels across NNNS exams. After control for confounders, associations with exposure groups emerged for all four NNNS subscales in the overall and sex-stratified samples, except for Attention for daughters and Lethargy for sons. Associations were negative for Self-Regulation (*p*s<.001, . 014, .002, respectively) and Attention (*p*s< .001, .177, .029) and positive for Handling (*p*s< . 001, .002, .006) and Lethargy (*p*s<.043, .023, .754).

3.3. Impact of MJ+TOB and TOB-exposure on NNNS Self-Regulation.

As shown in Table 2 and Figure 2A, both MJ+TOB-exposed and TOB-exposed infants showed significantly attenuated self-regulation over the first postnatal month vs. unexposed infants (*p*s< .03). Using an estimated residual SD of .70 units for the unexposed group, MJ +TOB-exposed infants showed nearly twice the impact on self-regulation vs. unexposed infants than was shown for TOB-exposed infants. MJ+TOB-exposed infants showed a .357

unit decrease (95% CI=.173-.541, p<.001) vs. unexposed infants, and a .185 unit decrease (95% CI=.007-.363, p=.043) vs. TOB-exposed infants. TOB-exposed infants showed a .172 unit (95% CI=.023-.321, p=.025) decrease vs. unexposed infants.

As shown in Table 2 and Figure 3A, stratifying by infant sex revealed a significant (.318 unit) decrease in self-regulation from TOB-only exposure vs. no exposure for sons (p<.003), but not daughters (p=.541). Effects of MJ+TOB vs. no exposure were significant for both sexes (ps<.005), but slightly more pronounced for daughters vs. sons (.426 vs .351 unit decreases). Finally, daughters (p=.011) but not sons (p=.786) showed a significant difference (.357 unit decrease) in the impact of MJ+TOB vs. TOB-only exposure on self-regulation.

3.4. Impact of MJ+TOB and TOB-exposure on NNNS Handling.

As shown in Table 2 and Figure 2B, both MJ+TOB-exposed and TOB-exposed infants showed significantly increased need for external handling over the first postnatal month vs. unexposed infants. Based on an estimated residual SD of .60 units in the logarithmic scale for the unexposed group, MJ+TOB-exposed infants showed nearly 2X the impact on handling vs. unexposed infants than did TOB-exposed infants. MJ+TOB-exposed infants showed a 32.1% increase in need for handling vs. unexposed infants (95% CI=16.2%-50.2%, p<.001) and an 12% increase vs. TOB-exposed infants (95% CI=.99–1.26, p=.066). TOB-exposed infants showed an 18.1% increase vs. unexposed infants (95% CI=6.0%-31.5%, p=.003).

As shown in Table 2 and Figure 3B, stratifying by infant sex revealed a significant (27%) increase in need for external handling from TOB-only exposure vs. no exposure for sons (p<.003), but not daughters (p=.178). Effects of MJ+TOB vs. no exposure were significant for both sexes (ps<.02), but were more pronounced for daughters vs. sons (40% vs. 27% increases). Finally, daughters (p=.007), but not sons (p=.963) showed a significant difference (26% increase) in the impact of MJ+TOB vs. TOB-only exposure on need for handling.

3.5. Impact of MJ+TOB and TOB-exposure on NNNS Attention.

As shown in Table 2 and Figure 2C, both MJ+TOB-exposed and TOB-exposed infants showed significantly decreased attention over the first postnatal month vs. unexposed infants (ps<.02). Based on an estimated residual SD of 1.41 units for the Control group, MJ +TOBexposed infants showed a .626 unit decrease in attention (95% CI=.197–1.055, p=.005) vs. unexposed infants, while TOB-exposed infants showed a .441 unit decrease (95% CI =.081-.802, p=.017). Although differences between MJ+TOB-exposed vs. TOB-exposed infants did not attain significance (p=.371) the impact of MJ+TOB was approximately 42% greater than the impact of TOB alone.

As shown in Table 2 and Figure 3C, stratifying by sex revealed a significant (.585 unit) decrease in attention from TOB-only exposure vs. no exposure for sons (p=.008), but not daughters (p=.420). MJ+TOB exposure vs. no exposure led to a trend toward decreased attention for daughters (.674 unit decrease; p=.063), but not sons (p=.113). Neither daughters nor sons showed significant differences between MJ+TOB and TOB-only exposure on attention (ps>.25).

3.6. Impact of MJ+TOB and TOB-exposure on NNNS Lethargy.

As shown in Table 2 and Figure 2D, MJ+TOB-exposed infants showed a 15% (95% CI = 3%-28%, p=.014) increase in lethargy over the first postnatal month vs. unexposed infants. TOB-exposed infants showed a trend toward increased lethargy vs. unexposed infants (p=.098). A residual SD of .39 units in the logarithmic scale was estimated for the unexposed group. Although no significant differences between MJ+TOB vs. TOB-exposed infants emerged (p=.256), the impact of MJ+TOB was 75% greater than TOB alone. As shown in Table 2 and Figure 3D, stratifying by infant sex revealed significant increases in lethargy from TOB-only exposure (17%) and MJ+TOB exposure (22%) vs. no exposure for daughters (ps<.05) but no effects of MJ+TOB or TOB-only for sons (ps>.45). No significant difference between MJ+TOB and TOB-only exposure emerged for daughters or sons for lethargy (ps>.55).

4. Discussion

We found a significant impact of prenatal co-exposure to marijuana and tobacco (MJ+TOB) on newborn neurobehavior using the NNNS, a neurologic and behavioral examination sensitive to subtle alterations in behavior in substance-exposed infants (Lester et al., 2004; Tronick and Lester, 2013). Specifically, MJ+TOB-exposed infants showed lower ability to self-soothe (NNNS Self-regulation) and attend to stimuli (NNNS Attention), and lower motor tone and inactivity (NNNS Lethargy), and greater need for external soothing (NNNS Handling) versus unexposed infants over the first postnatal month. Despite low levels of MJ co-use and similar TOB use levels between MJ+TOB and TOB groups, MJ+TOB co-exposure was associated with nearly double the impact on infant self-soothing and need for examiner soothing versus TOBexposure alone, and with a 42–75% increased impact on infant attention and lethargy versus TOB-exposure alone. Finally, we found sex-specific effects of MJ+TOB; such that effects of coexposure on self-soothing, need for external soothing, attention, and lethargy were more pronounced for daughters versus sons.

NNNS Self-Regulation measures newborns' capacity to self-soothe, or their ability to organize motor activity, physiology, and state in response to manipulation and stimulus presentations during the exam. Conversely, NNNS Handling measures newborns' need for external soothing, or their need for intervention from the examiner to soothe the infant and assist the infant in maintaining a quiet, alert state. MJ+TOB co-exposure resulted in significant decreases in self-soothing and increases in need for examiner soothing versus no substance exposure. Moreover, MJ+TOB co-exposure was associated with nearly 200% increased impact versus TOB exposure alone on self-soothing and need for examiner soothing. Results complement a recent MJ+TOB co-exposure study which revealed associations between coexposure and less adaptive autonomic regulation in nine-month old infants (Eiden et al., 2018). Results also complement prior studies of TOB-exposure alone, which showed increased irritability, alterations in regulatory processes and increased need for external soothing across the first postnatal month (Espy et al., 2011; Stroud et al., 2009a; Stroud et al., 2009b; Yolton et al., 2009). Our findings are also consistent with some prior prenatal MJ exposure studies that revealed increases in irritability and decreases in self-regulation in the early newborn period (de Moraes Barros et al., 2006; Fried, 1980; Fried and

Makin, 1987). Our newborn findings are inconsistent with a prior co-exposure study focused on 9-month-old infants, demonstrating no direct effects of prenatal MJ+TOB on infant regulation (Schuetze et al., 2018). Thus, it is possible that MJ+TOB effects demonstrated in the current study are transitory—potentially related to withdrawal processes or neural development specific to the newborn period—and dissipate by later infancy. Future studies are needed to replicate current findings and to elucidate the evolution of prenatal co-exposure effects over the first postnatal year.

Prenatal co-exposure to MJ+TOB also resulted in significant decreases in newborn attention and increases in lethargy versus no substance exposure. NNNS Attention is a measure of orientation to animate and inanimate auditory and visual stimuli; NNNS Lethargy is a measure of infant lethargic behavior or low levels of motor, state, and physiologic reactivity. Although differences between MJ+TOB versus TOB-only exposure were not statistically significant for either attention or lethargy, MJ+TOB exposure was associated with a 42% increased impact on newborn attention and a 75% increased impact on lethargy. Effects on newborn attention complement prior cross-sectional and longitudinal studies of prenatal TOB (Espy et al., 2011; Mansi et al., 2007). Although effects of prenatal TOB have been somewhat inconsistent in early infancy (Law et al., 2003; Stroud et al., 2009b; Yolton et al., 2009), one of the more consistent long-term effects of prenatal TOB is its association with child attention deficits, ADHD, and deficits in executive function (Huang et al., 2018; Micalizzi and Knopik, 2017). In contrast, prior studies of prenatal MJ did not show effects on attention in the newborn period (de Moraes Barros et al., 2006; Fried, 1980; Fried and Makin, 1987), although effects on long-term attention and executive function deficits have been shown (El Marroun et al., 2011; Smith et al., 2006; Smith et al., 2016).

We can speculate about potential mechanisms underlying effects of MJ+TOB on infant development. First, it is possible MJ+TOB co-exposure effects are due to increased exposure to TOB/cigarettes in the MJ+TOB group. However, we found nearly identical average cigarettes per day in the MJ+TOB versus the TOB-only group (M=7±6 per day for both groups). Similarly, it is possible that co-exposure effects are due to increased exposure to nicotine and/or combustion. The majority of MJ+TOB users in our sample endorsed smoking MJ (e.g., joints, bowls, blunts) versus other methods of use (edibles, vaping) suggesting increased exposure to combustion. Further, approximately 42% endorsed use of blunts (partially or fully hollowed cigar wrappers filled with marijuana), which contain measurable amounts of nicotine and increase in carbon monoxide levels relative to joints (Cooper and Haney, 2009; Peters et al., 2016). However, we found no differences between MJ+TOB and TOB groups in 3rd trimester cotinine (nicotine metabolite) or carbon monoxide levels (marker of exposure to combustion). Nonetheless, because most MJ use took place during 1st trimester in this sample, it is possible that effects of co-use may be related to increased nicotine or combustion exposure in early gestation.

Another possibility is that exposure to MJ+TOB (vs. TOB only) may not only disrupt nicotinic pathways, but also additional pathways in the fetal brain, leading to more profound alterations in neurodevelopment. THC crosses the placenta and exerts its biological functions through binding to cannabinoid receptors (Type 1: CB1, and Type 2: CB2) in the endocannabinoid system, which are present in early fetal development (Bailey et al., 1987;

Matsuda et al., 1990; Munro et al., 1993; Parsons and Hurd, 2015; Richardson et al., 2016). The fetal endocannabinoid system regulates several aspects of neural development, including neurogenesis, neuronal migration, neurite outgrowth and axonal pathfinding (Vitalis et al., 2008). Preclinical studies have revealed pernicious effects of prenatal THC on neuronal development via disruption of endocannabinoid signaling pathways (de Salas-Quiroga et al., 2015; Szutorisz et al., 2014; Tortoriello et al., 2014). Synergistic effects of prenatal TOB/nicotine and MJ/THC on glucocorticoid and reward signaling pathways and/or epigenetic pathways are also plausible (del Arco et al., 2000; Morris et al., 2011; Szutorisz and Hurd, 2016, 2018).

Finally, it is possible that co-exposure effects on offspring outcomes are due to differences in characteristics of MJ+TOB co-users vs. sole TOB users and controls. Although relevant demographic characteristics were statistically controlled, it is possible that there were unmeasured genetic or personality differences that may lead to both maternal MJ+TOB co-use and alterations in infant neurobehavior. Future studies with genetically sensitive designs are needed to tease apart interactions between maternal exposures and maternal characteristics/ genetics on offspring neurobehavioral outcomes (Bidwell et al., 2016; D'Onofrio et al., 2014; Fang et al., 2010).

Our exploratory analyses of sex-specific effects of prenatal MJ+TOB revealed an overall more pronounced impact of co-exposure on newborn neurobehavior for daughters versus sons. Specifically, although effects of MJ+TOB on self-regulation and need for external handling were statistically significant for both sexes, effects were 20% and 50% greater for daughters than sons, respectively. For attention and lethargy, effects of co-exposure were significant for daughters only--not sons. Daughter-specific effects of MJ+TOB complement a study of prenatal MJ and attention and aggression in 18-month olds in which MJ effects were only significant for daughters, and the majority of MJ-exposed infants were co-exposed to prenatal TOB (El Marroun et al., 2011). In contrast, we found that effects of prenatal TOB alone on newborn neurobehavior were specific to sons for most neurobehavioral scales. In particular, prenatal TOB was associated with decreased self-regulation, increased need for handling, and decreased attention in sons but not daughters. Son-specific prenatal TOB effects on newborn behavioral dysregulation are consistent with prior studies highlighting son-specific prenatal TOB effects on risk for offspring disruptive behavior disorders in older offspring (Brennan et al., 2002; Fergusson et al., 1998; Weissman et al., 1999). Although replication of the current pattern of sexspecific findings is needed, we can speculate on mechanisms. Potential mechanisms may include: (a) sex hormone modulation of effects of THC+nicotine vs nicotine on fetal neuronal development, (b) sexual differentiation of emerging fetal brain structures and function may lead to differential impact of THC+nicotine vs nicotine by fetal sex, (c) sex differences in placental structure and function may modulate passage of THC+nicotine vs nicotine to the developing fetus, (d) sex differences in genetic or epigenetic pathways that regulate response to environmental cues, and (e) fetal sex-influenced differences in the maternal hormonal milieu (Clifton, 2010; Cross et al., 2017; DiPietro and Voegtline, 2017; Sundram, 2006). Large-scale longitudinal studies powered to investigate interactions of substance exposures and offspring sex are needed to delineate sex-specific developmental trajectories of coherent, narrow band phenotypes (Wakschlag et al., 2018) following prenatal co-exposures as well as underlying mechanisms. Comprehensive

theories are also needed to better integrate relatively inconsistent patterns of findings with respect to offspring sex within and across exposures, offspring phenotypes, and even species (e.g., (Sandman et al., 2013).

We acknowledge several additional limitations that provide directions for future research. Key limitations relate to our use of a sample selected to understand maternal tobacco use—including the small number of MJ+TOB co-users (n=24) and low levels of MJ use. However, that MJ+TOB co-use effects emerged despite the small co-use sample and low co-use levels suggests that even larger effects might emerge in a larger sample with greater levels and more prolonged MJ co-use. Further, although we compared the impact of prenatal MJ+TOB coexposure to TOB-only exposure, we did not have a MJ-only exposure group. Future studies need to include both TOB-only and MJ-only groups to determine the unique and synergistic impacts of MJ and TOB exposures on offspring development. Finally, the present analyses focused on group differences in the impact of any MJ+TOB and TOB-only exposure on infant neurobehavior. Future dose-response studies are needed to determine the quantitative impact of MJ/THC and TOB/nicotine on infant neurobehavior.

Findings from the present study highlight the importance of explicitly characterizing the impact of substance co-exposures on infant outcomes. While single exposure studies (where effects of other substances are controlled through group inclusion criteria and/or statistical techniques) are needed to determine specific effects of any given substance, studies designed to investigate co-exposures also offer potential to inform obstetric providers and pregnant mothers regarding offspring outcomes following “real-world” co-use behaviors. Future studies are also needed to explicitly characterize potential additive or multiplicative effects of additional substance exposures and non-substance exposures including environmental toxins, poverty, stress, and mental health problems (Clark et al., 2016; Stroud et al., 2014b).

Our findings also have implications for intervention and prevention efforts. The first month is an important period for development of mother-infant attachment. The combination of a lethargic infant requiring additional external soothing and a co-using mother with fewer resources and parenting skills could disrupt maternal-infant interactions during this critical period. Alterations in newborn behavior may themselves portend adverse long-term outcomes; however, more likely is that subtle differences in newborn behavior in the context of a less resourced parent may lead to a maladaptive cycle of continued behavioral dysregulation, further disruptions in maternal-infant attachment, and eventually, long-term adverse offspring outcomes (Beeghly et al., 2016; Beeghly and Tronick, 1994; Blackwell et al., 1998; Lester et al., 2009).Results highlight the need for early identification, intervention and education efforts for parents of exposed/co-exposed infants to prevent disruptions in early mother-infant attachment and to assist in facilitating self-regulatory skill development. Results also highlight the need to assess MJ co-use in pregnant TOB users and to educate pregnant TOB-users regarding potential risks of MJ co-use. The adverse effects of prenatal TOB have received a great deal of public health attention (England et al., 2017b; Haviland et al., 2004; Orleans et al., 2004); however, despite increasing availability and use of MJ, both pregnant women and obstetric providers report a dearth of available information regarding effects of prenatal MJ use on mothers and offspring (Holland et al., 2016a; Holland et al.,

2016b; Jarlenski et al., 2016). Novel interventions are also needed to address both TOB use and MJ co-use.

4.1. Conclusions

Our findings suggest that the profile of a MJ+TOB co-exposed infant in the newborn period includes greater difficulty in self-soothing, greater need for external soothing, poorer attention to stimuli, and greater lethargy. Alterations in newborns' ability to self-soothe and need for external soothing were nearly 2X greater for MJ+TOB exposure versus TOB exposure alone. Results highlight additional risks of dual exposure to MJ+TOB versus TOB exposure alone and the importance of explicitly characterizing prenatal substance exposures in concert and in context. Results also highlight the need for intervention efforts to address MJ co-use in pregnant TOB users and for early identification of co-exposed infants.

Difference

ACKNOWLEDGEMENTS

We are also grateful to Cheryl Boyce, Program Officer, for her support of this work and this field. to: We are grateful to Cheryl Boyce and Nicolette Borek, NIH Program Officers, for their support of this work and this field.

ROLE OF THE FUNDING SOURCE

Preparation of this manuscript and data collection was supported by the National Institutes of Health (R01 DA019558 and R01 DA044504 to L.R.S.). The funding agencies had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the pape

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HIGHLIGHTS

- Investigated the impact of marijuana and tobacco co-use in pregnancy on newborn behavior.
- Newborns exposed to both marijuana and tobacco showed decreased ability to self-soothe and attend to stimuli.
- Co-exposed newborns also needed more external soothing and were more lethargic.
- Effects of co-exposure were worse for daughters than for sons.
- Intervention efforts to address marijuana co-use in pregnant tobacco users are needed.

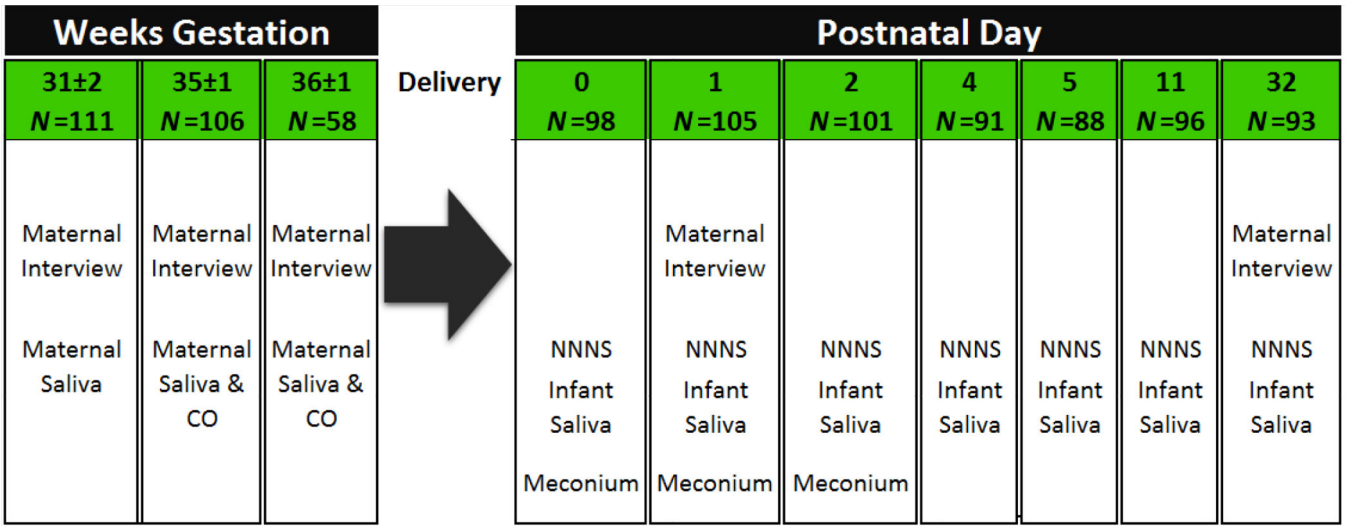

Figure 1.

Overview of the Behavior and Mood in Babies and Mothers (BAM BAM) study. **Note:** CO=Breath Carbon Monoxide assessment; NNNS=NICU Network Neurobehavioral Scale.

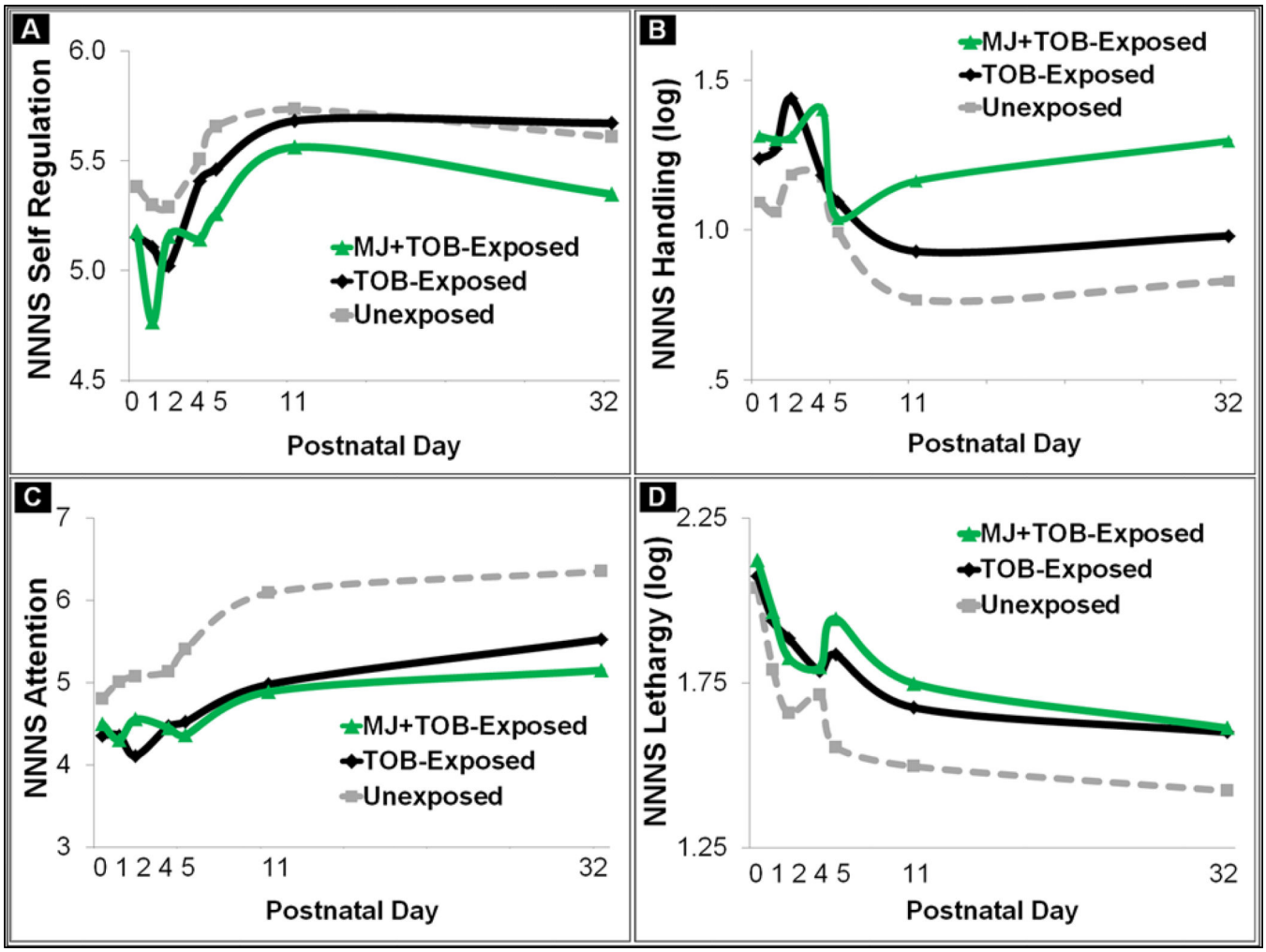

Figure 2.

Infant Neurobehavior over the first Postnatal Month in MJ+TOB-exposed, TOBexposed, and unexposed infants: (a) NICU Network Neurobehavioral Scale (NNNS) SelfRegulation, (b) NNNS Handling, (c) NNNS Attention, (d) NNNS Lethargy. The NICU Network Neurobehavioral Scale (NNNS) was administered up to 7 times over the first postnatal month at days 0 (*M*=8 hours), 1, 2, 4, 5, 11, and 32. NNNS Lethargy and NNNS Handling were modeled in the logarithmic scale.

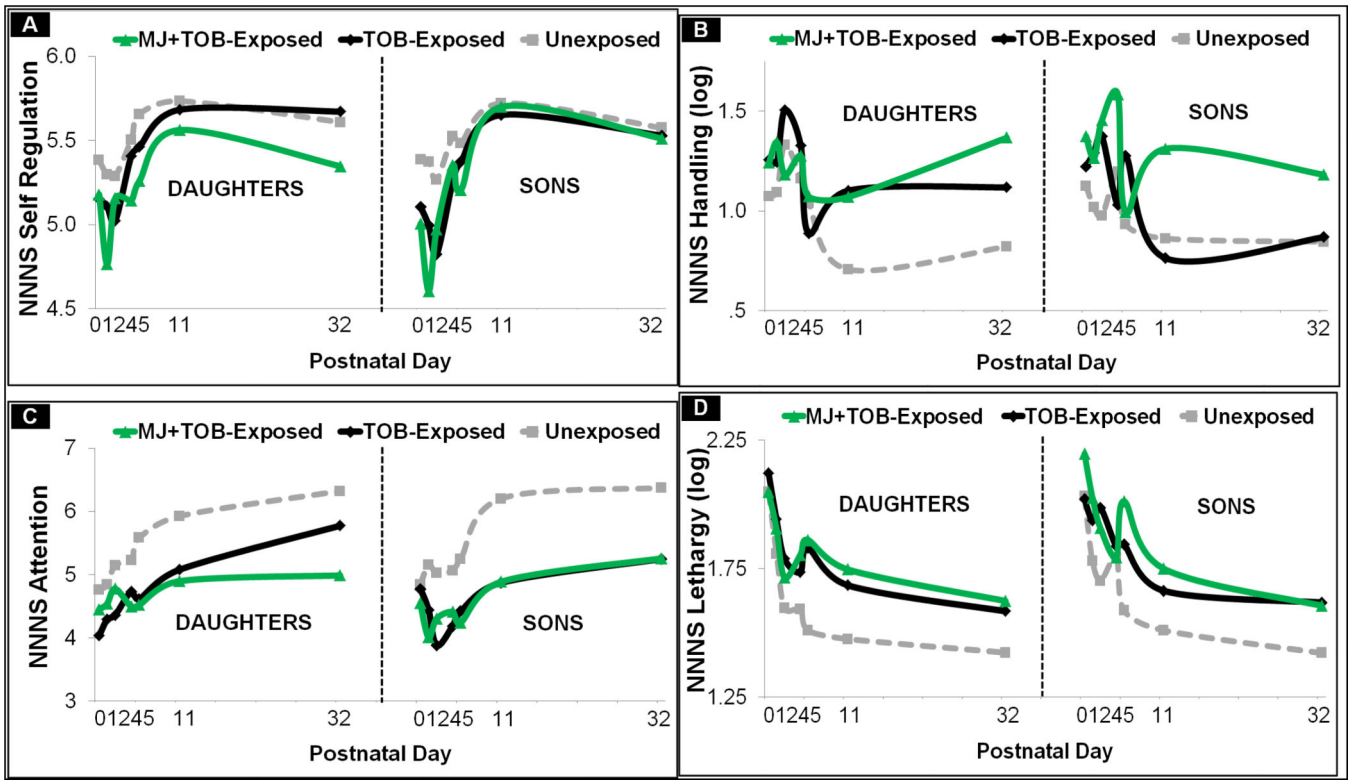

Figure 3.

Infant Neurobehavior over the first Postnatal Month in MJ+TOB-exposed, TOBexposed, and unexposed daughters and sons: (a) NICU Network Neurobehavioral Scale (NNNS) Self-Regulation, (b) NNNS Handling, (c) NNNS Attention, (d) NNNS Lethargy.

Table 1.

Maternal and infant characteristics by tobacco (TOB) and marijuana (MJ) exposure group and full sample.

	Controls (*n*=42) Mean (SD)/ %	TOB (*n*=45) Mean (SD)/ %	MJ+TOB (*n*=24) Mean (SD)/ %	Total (*n*=11) Mean (SD)/ %
Maternal Characteristics				
Age (years)	25 (6)	24 (4)	25 (4)	25 (5)
Race/Ethnicity (% Non-Hispanic White)	42%	53%	42%	46%
Low SES[1]	20%	47%	65%	40%***
Gravida	2.3 (1.6)	2.9 (2.2)	2.6 (1.4)	2.6 (1.8)
Parity	1.0 (1.2)	1.2 (1.5)	1.1 (1.4)	1.1 (1.4)
Weight gain (pounds)[2]	33 (17)	27 (18)	32 (13)	31 (17)
Alcohol Use (>1 drink/week)	0%	4%	17%	5%*
Caffeine Use (>200 mg/day caffeine)[3]	5%	39%	21%	22%***
High ETS Exposure (>1 hour/day)[4]	2%	59%	29%	40%***
Gestational Medical Conditions[5]	7%	22%	17%	15%
Depressive Symptoms[6]	2 (3)	5 (5)	6 (6)	4 (5)**
Tobacco Use (cigs/day)[7]	0 (0)	7.3 (6.2)	6.8 (5.4)	---
Maternal Cotinine per day (ng/mL)[7]	0 (0)	96 (111)	75 (91)	---
Maternal Carbon Monoxide (ppm)[7]	1 (1)	6 (5)	4 (3)	---
Infant Characteristics				
Sex (% female)	40%	51%	46%	46%
Delivery Mode (% vaginal delivery)	76%	78%	79%	77%
Gestational age at birth (weeks)	40 (1)	40 (1)	40 (1)	40 (1)
Small for gestational age[8]	2%	7%	4%	5%
Apgar score (> 8 at 5 minutes)	90%	98%	96%	95%
Any breastfeeding	81%	56%	46%	62%
ETS Exposure: saliva cotinine (ng/ml)[9]	1 (2)	12 (21)	11 (23)	8 (18)

*NOTE:$p<.05$;

**$p<.01$,

***$p<.001$.

[1]Based on a score of 4 or 5 on the Hollingshead Index.

[2]Weight gain in pounds between pre-pregnancy and 35±1 weeks.

[3]Equivalent of two cups of coffee per day.

[4]Hours of environmental tobacco smoke exposure per week measured by structured interview.

[5]e.g., gestational hypertension, gestational diabetes.

[6]Score on 21-item Hamilton Depression Rating Scale.

[7] No significant differences between tobacco-only and marijuana+tobacco groups

[8] Birthweight <10th percentile for gestational age.

[9] Environmental Tobacco Smoke exposure measured by infant saliva cotinine at postnatal day 32 (ng/ml).

Table 2.

Impact of marijuana+tobacco (MJ+TOB) co-use and sole tobacco (TOB) use on newborn neurobehavior over the first postnatal month for the full sample (n=111) and for daughters (n=51) and sons (n=60).

Predictor Variables	Full Sample			Daughters			Sons		
	β	*SE*	*p*	*β*	*SE*	*p*	*β*	*SE*	*p*
Self-Regulation[1]									
Intercept	5.334	.219	<.001	5.144	.297	<.001	5.543	.317	<.001
Infant age[6]	.092	.023	<.001	.090	.033	.007	.098	.032	.002
Time since feeding[7]	−.020	.035	.569	.040	.046	.387	−.074	.051	.147
Any Breastfeeding	−.193	.073	.008	−.203	.107	.058	−.232	.099	.020
Tobacco	**−.172**	**.076**	**.025**	−.069	.112	.541	**−.318**	**.106**	**.003**
Marijuana + Tobacco	**−.357**	**.094**	**<.001**	**−.426**	**.151**	**.005**	**−.351**	**.119**	**.003**
MJ+TOB vs. TOB									
Difference	***−.185***	***.091***	***.043***	***−.357***	***.140***	***.011***	*−.033*	*.122*	*.786*
Handling[2,5]									
Intercept	.983	.180	<.001	.960	.244	<.001	.956	.264	<.001
Infant age[6]	−.065	.018	<.001	−.075	.025	.003	−.053	.026	.039
Time since feeding[7]	.053	.030	.079	.062	.042	.141	.044	.043	.313
Any Breastfeeding	.140	.050	.005	.177	.071	.013	.151	.072	.038
Tobacco	**.166**	**.055**	**.003**	.103	.076	.178	**.242**	**.080**	**.003**
Marijuana + Tobacco	**.278**	**.066**	**<.001**	**.334**	**.092**	**<.001**	**.237**	**.094**	**.012**
MJ+TOB vs. TOB	***.112***	***.061***	***.066***	***.231***	***.086***	***.007***	*−.004*	*.087*	*.963*
Attention[3]									
Intercept	3.455	.439	<.001	2.272	.565	<.001	4.390	.612	<.001
Infant age[6]	.337	.052	<.001	.400	.072	<.001	.296	.068	<.001
Time since feeding[7]	.156	.068	.023	.339	.082	<.001	.002	.099	.983
Infant ETS[8]	−.010	.004	.023	−.006	.008	.491	−.018	.005	.001
Depression Score[9]	−.058	.016	<.001	−.041	.029	.153	−.076	.021	<.001
Tobacco	**−.441**	**.184**	**.017**	−.257	.318	.420	**−.585**	**.219**	**.008**
Marijuana + Tobacco	**−.626**	**.219**	**.005**	**−.674**	**.361**	**.063**	−.465	.292	.113
MJ+TOB vs. TOBDifference	*−.185*	*.207*	*.371*	*−.417*	*.368*	*.259*	*−.119*	*.261*	*.649*
Lethargy[4,5]Intercept	2.447	.119	<.001	2.426	.175	<.001	2.418	.161	<.001
Infant age[6]	−.132	.013	<.001	−.134	.019	<.001	−.128	.018	<.001
Time since feeding[7]	−.055	.020	.006	−.054	.030	.078	−.052	.027	.054
Infant ETS[8]	.002	.001	.031	−.001	.002	.700	.005	.001	.001
Depression Score[9]	.013	.004	.002	.008	.006	.197	.019	.006	.001
Tobacco	.077	.047	.098	**.158**	**.070**	**.025**	.027	.062	.664

Marijuana + Tobacco	**.136**	**.055**	**.014**	**.201**	**.079**	**.011**	.059	.079	.455
MJ+TOB vs. TOBDifference	*.058*	*.051*	***.256***	*.044*	*.074*	*.553*	*.032*	*.072*	*.656*

Note: Reference group is unexposed infants for the overall model. Red, italicized coefficients show differences between MJ+TOB versus TOB-exposed infants.

[1]NICU Network Neurobehavioral Scale (NNNS) Self-Regulation measures the infant's capacity to organize motor activity, physiology, and state in response to manipulation and stimulus presentations throughout the exam;

[2]NNNS Handling is a measure of need for intervention from the NNNS examiner to soothe the infant and assist the infant in maintaining a quiet, alert state.

[3]NNNS Attention is a measure of orientation to animate and inanimate auditory and visual stimuli.

[4]NNNS Lethargy is a measure of low levels of motor, state and physiologic reactivity.

[5]NNNS Lethargy and NNNS Handling were natural log transformed.

[6]Infant age (measured in hours).

[7]Time since feeding (measured in mins).

[8]Infant Environmental Tobacco Smoke (ETS) exposure measured by saliva cotinine (ng/ml).

[9]Maternal depressive symptoms on 21-item Hamilton Depression Rating Scale.