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Determining the Impact of Prenatal Tobacco Exposure on Self-regulation at Six Months

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Abstract

The goal of the present study was to examine the effects of maternal smoking during pregnancy on infant self-regulation, exploring birth weight as a mediator and sex as a moderator of risk. A prospective sample of 218 infants was assessed at 6 months of age. Infants completed a battery of tasks assessing working memory/inhibition, attention, and emotional reactivity and regulation. Propensity scores were used to statistically control for confounding risk factors associated with maternal smoking during pregnancy. After prenatal and postnatal confounds were controlled, prenatal tobacco exposure was related to reactivity to frustration and control of attention during stimulus encoding. Birth weight did not mediate the effect of prenatal exposure, but was independently related to reactivity and working memory/inhibition. The effect of tobacco exposure was not moderated by sex.

Keywords

Prenatal tobacco exposure; infancy; self-regulation; attention; emotion regulation

Self-regulation is the ability to regulate one's thoughts, actions, and emotions, typically in service of a goal (Bell & Deater-Deckard, 2007). Self-regulatory skills are linked to academic and social success in childhood and reduced risk of later difficulties such as externalizing behavior and substance abuse (Blair & Diamond, 2008; Wills, Pokhrel, Morehouse, & Fenster, 2011). One of the most common, preventable risk factors for

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childhood difficulties with self-regulation is prenatal tobacco exposure (PTE) (Huijbregts, Warren, de Sonneville, & Swaab-Barneveld, 2008; Mezzacappa, Buckner, & Earls, 2011; Noland et al., 2005). Despite increasing awareness of health risks, smoking during pregnancy remains common: in 2004, 18.5% of pregnant women in the US smoked, with rates as high as 30% in some subpopulations (Centers for Disease Control and Prevention, 2005). Many studies have verified PTE's association with childhood self-regulation problems, but less is known about PTE's effects on self-regulation in infancy, when these skills first emerge. The goal of the present study was to study PTE's effects on infant development by measuring emergent self-regulation midway through the first year of life.

The task of estimating PTE's precise effect on any outcome is complicated by a number of persistent issues. First, infants with PTE experience other genetic and environmental risk factors at a higher rate than their non-exposed peers, and thus it is important to account for these potential confounds (D'Onofrio et al., 2003; Fang et al., 2010). Second, it is difficult to determine whether effects are attributable to nicotine's direct influence on neurodevelopment or whether the effects are indirect, via mediating factors such as low birth weight (Nigg & Breslau, 2007). Third, it is unclear whether the effects of PTE are the same for all infants or whether some infants are more vulnerable. There are indications that gender may act as a moderator, such that prenatally-exposed boys demonstrate poorer outcomes than girls (Schuetze, Lopez, Granger, & Eiden, 2008). The present study was designed with these issues in mind: PTE and other pre-, peri-, and post-natal risk factors were measured during and after pregnancy to enable us to assess PTE's effect on self-regulation at 6 months over and above the contribution of confounding risks, birth weight was tested as a mediator of PTE's effects, and we explored gender differences in risk-outcome relationships.

PTE and Infant Self-regulation

Numerous studies spanning several decades have found differences in arousal, attention, reaction to stress, and soothability between tobacco-exposed (TE) and non-exposed (NE) neonates (Espy et al., 2011; Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1984; Mansi et al., 2007; Stroud et al., 2009). In contrast, there is a relative dearth of research examining the effects of PTE on infant self-regulation beyond the first month of life. This gap is unfortunate, because infancy is marked by increasing top-down control of attention, behavior, and emotions, and therefore, relative to neonatal differences, self-regulatory problems observed midway through the first year may be more informative about children's later development, when PTE is associated with problems regulating attention and behavior (Mezzacappa et al., 2011; Noland et al., 2005; Wakschlag, Leventhal, Pine, Pickett, & Carter, 2006).

Recently, researchers have begun to address this gap, and have found continued difficulties with affect and attention. Willoughby and colleagues (2007) found that PTE was associated with more negative and less positive affect during a home visit when infants were 6–8 months old, and, for boys, lower levels of attention, approach, and gross motor movements. Similarly, at age 7 months, PTE was associated with higher negative affect on the basis of maternal ratings (Schuetze & Eiden, 2007) and greater peak cortisol response to an arm restraint stressor, particularly in boys (Schuetze et al., 2008). In a small sample of tobacco-

exposed 9-month-olds, who served as the control group in a study of cocaine use during pregnancy, the level of tobacco exposure was correlated with distractibility during familiarization in a novelty preference task (Gaultney, Gingras, Martin, & DeBrule, 2005).

More research is necessary to replicate these findings and shed light on the mechanisms that account for relations between PTE and infant and child outcomes. It is important to consider the potential mediating role of birth outcomes, because PTE contributes to the incidence of low birth weight due to the anoxic effects of carbon monoxide, nicotine, and other constituents of tobacco smoke (Cornelius & Day, 2009), and low birth weight is associated with an increased risk for behavioral disorders and cognitive dysfunction (Pharoah, Stevenson, Cooke, & Stevenson, 1994; Taylor, Minich, Klein, & Hack, 2004). However, there is reason to suspect that PTE might also have a direct impact on the neural substrates of self-regulation. The strongest evidence for this link comes from animal studies showing that prenatal nicotine exposure disrupts the timing of neuronal replication and differentiation, permanently altering the structure of the prenatally-exposed brain (Chen, Parker, Matta, & Sharp, 2005; McFarland, Seidler, & Slotkin, 1991) with downstream effects on neural circuits dependent on dopamine, norepenephrine, and serotonin (Muneoka et al., 1997; for a review, see Dwyer, McQuown, & Leslie, 2009). PTE may influence self-regulation via direct *and* mediated pathways: Nigg and Breslau (Nigg & Breslau, 2007) found that PTE had a direct effect on disruptive behavior disorders, whereas its relation with attention problems was mediated by birth outcomes.

Another important question relates to sex differences in vulnerability to PTE. It is well documented that boys are more vulnerable to a variety of prenatal and perinatal insults, although the reasons for this sex difference are not yet understood (Elsmén, Steen, & Hellström-Westas, 2004; Moe & Slinning, 2001). Studies have found stronger effects of PTE for boys on infant behavioral outcomes (Schuetze et al., 2008; Willoughby et al., 2007), childhood conduct problems (Wakschlag & Hans, 2002), and hyperactivity in mice (Pauly, Sparks, Hauser, & Pauly, 2004). As such, it is important to consider the moderating role of sex when examining the relation between PTE and behavioral outcomes.

PTE and Confounding Risks

Because PTE is not, and cannot, be randomly assigned, we cannot draw causal conclusions regarding PTE's correlations with self-regulation. Psychological, sociodemographic, and genetic differences between women who do and do not smoke during pregnancy each likely contribute to observed differences. Women who smoke throughout pregnancy have more sociodemographic risk factors than women who do not smoke or quit during pregnancy (Woodby, Windsor, Snyder, Kohler, & DiClemente, 1999), and are more likely to be diagnosed with attention and behavior disorders (Flick et al., 2006). In an Australian twin study, 34% of the variance in smoking during pregnancy was related to genetic variability (Agrawal et al., 2008). Several studies have found that PTE's estimated effects on attention problems and antisocial behavior were reduced in magnitude or rendered statistically insignificant after taking genetic relatedness into account (D'Onofrio et al., 2008, 2010). These studies have some limitations, including retrospective smoking measurement, use of behavior ratings rather than direct assessment, and a wide age range in the child samples.

Nevertheless, they demonstrate that factors other than smoking during pregnancy contribute to the risk associated with PTE.

Most studies of PTE have attempted to account for confounding risk factors by statistically controlling for parental and contextual characteristics that are confounded with maternal smoking during pregnancy. Unfortunately, this approach has consequences for statistical power and the required sample sizes to detect the true effect. Recently, several studies have used propensity scores (PS) (McCaffrey, Ridgeway, & Morral, 2004; Rosenbaum & Rubin, 1983) to balance groups and control for confounding factors and selection bias. In PS estimation, those risk factors that empirically contribute to selection bias are identified and combined into a single metric using statistical models such as logistic regression (Rosenbaum & Rubin, 1983) or more robust statistical techniques such as generalized boosted models that model variables with non-normal distributions (Friedman, 2001; Imbens, 2003; McCaffrey et al., 2004). PS can then be used to correct for imbalances in the groups. In large samples (e.g., population studies), PS matching typically results in an adequate number of matched pairs despite loss of a large number of subjects. For moderate samples, it is often more feasible to use PS as a covariate in statistical models, particularly when the number of confounding variables is large and the power implications of participant loss in the matching process may be more severe (Ellis, Berg-Nielsen, Lydersen, & Wichstrøm, 2012; Fang et al., 2010).

Based on the reviewed evidence that risk factors contributing to maternal propensity to smoke during pregnancy may account for some observed associations between maternal smoking and child outcomes, the PS approach is well-suited conceptually to study PTE, and a growing number of researchers are doing so. For example, da Veiga and Wilder (2008) used PS matching to estimate more precisely the impact of PTE on birth weight and found a dose-response relation, where even light smoking was associated with a decrease in birth weight. Ellis and colleagues (2012) used a PS covariate to determine how PTE affected risk for psychiatric disorders in 4-year-old children. To date, two studies have applied a propensity score approach to infant self-regulation. Willoughby and colleages (2007) used PS matching to select a sample of non-exposed infants comparable to the tobacco-exposed group for analysis, and found pronounced differences in positive and negative affect, with smaller PTE effects on attention. Fang and colleagues (2010) included a PS covariate in models predicting birth weight and neonatal attention, and found that the effect of PTE on neonatal outcomes was larger in models that included PS, suggesting that background maternal differences masked the true effect of PTE.

The Present Study

The goal of the present study was to characterize the impact of PTE on emergent self-regulation at age 6 months. Self-regulation was assessed using a battery of tests drawn from the literature. We used hierarchical regression to model PTE's effect on self-regulation after adjusting for potential confounds. We also tested the hypotheses that (1) PTE's effects on self-regulation are mediated by fetal growth retardation due to anoxia, as indexed by birth weight, and (2) PTE's effects are moderated by infant sex, where boys are more vulnerable to the risk conferred by PTE than girls. Exposure was characterized prospectively using

maternal report with biochemical verification at three points in pregnancy. To improve the precision of our estimate of PTE's effect, we used PS as a covariate to control for confounding risks that differed between tobacco-exposed and non-exposed infants.

Method

Participants

The sample included 218 6-month-old infants (104 girls and 114 boys) and their mothers. Mothers were European American (86%), African American (7%), Native American (1%), or of more than one racial background (5%). Infants were European American (69%), African American (6%), or of more than one racial background (25%). Independent of race, 7% of women and 16% of infants were of Hispanic ethnic background. Mother-infant dyads were recruited from a cohort (N = 361) recruited during pregnancy (usually before 14 weeks) to study the effects of PTE on neonatal outcomes (Espy et al., 2011). Women were recruited at two Midwestern study sites, a small city and a rural tri-county area. Because cigarette smoking is associated with lower income and education, stratified enrollment procedures were used to minimize potentially confounding demographic differences between the smoking and non-smoking groups. Women with heavier smoking behavior were oversampled to ensure the full dose-response continuum. Women who reported binge alcohol use (≥ 4 drinks/occasion or ≥ 1.0 AA/day) prenatally also were excluded from participation, as were women who reported use of any illegal drugs, with the exception of occasional marijuana use (n = 25). Infants with birth complications known to affect developmental outcome (e.g., preterm birth < 35 weeks, neonatal seizures) were also excluded. Of the initial cohort or 361 infants, 99 infants were not eligible to participate in the present study because they were older than the target age of 6 months when the study was initiated (n = 82), their families had moved out of the area (n = 15), the mother no longer had custody (n = 1) or the infant was diagnosed with a neurological condition (n = 1). Of the remaining 262 infants, 218 (83.2%) participated; 12 (4.6%) missed appointments and could not be rescheduled within the time window; 8 (3.1%) declined to participate; 22 (8.4%) could not be located; and 2 (0.8%) were not scheduled due to administrative error. Mother-infant pairs who participated did not differ from those lost to follow-up in income, Hispanic ethnicity, infant sex, or maternal smoking status. Mothers who participated were older than those who did not, $t(260) = 3.85$, $p < .001$ (M = 26.1 vs. 23.5 years), more educated, $t(26) = 2.21$, $p = .03$ (M = 13.3 vs. 12.7 years), and more likely to be of European American background, $\chi^2(1, n = 277) = 9.09$, $p = .003$ (86% vs. 66%).

Procedures

Each infant was tested individually in a developmental laboratory setting by a trained research assistant, who was blind to the infant's prenatal exposure status. A battery of self-regulation tasks was administered in two sessions, in a fixed order to ensure that any potential carry-over effects were comparable across assessments. Adherence to experimental protocols was maintained by regular team meetings and session reviews with the first author. Between the sessions, mothers completed a telephone interview and a packet of questionnaires. Infants received a small toy and mothers received a gift card as compensation.

Prenatal Tobacco Exposure—Data on maternal smoking during pregnancy was collected as part of the initial study (Espy et al., 2011). At 14 and 28 weeks gestation and at delivery, mothers provide a month-by-month report of the number of cigarettes smoked per day using a modified timeline follow-back (TLFB) method (Sobell & Sobell, 1992), where dates were used to cue recall. TLFB assessments of smoking behavior have demonstrated reliability and validity, when compared with daily reports and biochemical indices (Brown et al., 1998). Maternal urine samples were collected at each interview and infant meconium was collected at birth. Biospecimens were analyzed for cotinine, a metabolite of nicotine. Any mother-infant pairs with urine cotinine values over 50 ng/mL (as recommended by US Drug Testing Laboratories), where the mother denied smoking, were included in the TE group, as it was not possible to determine whether these mothers were misrepresenting active, but intermittent, light smoking or were exposed to substantial environmental tobacco smoke (ETS).

Arm Restraint (adapted from Stifter & Fox, 1990)—This task was used to assess emotion regulation in response to moderate frustration. The infant was seated in a high chair, and the examiner (positioned behind the chair) gently but firmly held the infant's arms for up to 2 minutes; if infants became distressed, arms were released after 20 seconds of hard crying. Following the restraint phase, the infant was given a 1-minute period to self-soothe; for infants who failed to self-soothe, the task was discontinued after 20 seconds. The mother was in the room during the task, but was given a questionnaire to fill out and was instructed not to interact with her infant. Infant behavior was coded from video in Observer 5.12 (Noldus, Wageningen, Netherlands), by research assistants who were blind to infant exposure status. Infant reactivity was coded throughout both task phases based on facial expression, crying, and body movements (coded as neutral, mildly reactive, highly reactive). Specific regulatory behaviors were also coded (looking to the caregiver, attending to other stimuli in the room, and avoidance behaviors; self-soothing could be coded during the recovery phase only). To check interrater reliability, 20% of sessions were coded independently (*M* agreement = 92% for reactivity, 82% for regulatory behaviors). Sixteen infants had missing data for this task because of fussiness ($n = 4$), examiner error ($n = 7$), and audiovisual problems ($n = 5$). Seven additional infants had missing data for the recovery phase because of fussiness ($n = 5$) and examiner error ($n = 2$).

To reduce the number of dependent measures, principal components analyses were conducted separately in SAS's *Proc Factor* for the Restraint and Recovery phases (summarized in Supplementary Table 1). Variables analyzed were the proportion of time infants displayed each reactivity level and regulatory behavior. The oblimin rotation was applied, allowing components to be intercorrelated. Eigenvalues (> 1) and inspection of scree plots were used to determine the number of components to retain, yielding two components for each phase. In the Restraint phase, the components captured 64.7% of the variance in the original scores; nonnegative vocalizations did not load highly on either component, with resulting low communality (9.9%). The first component reflected infant negative reactivity, with positive loadings from mild and high reactivity and avoidance, and negative loadings from neutral affect and orientation to stimuli in the room. The second component reflected the infant's tendency to orient to the mother, with negative loadings

from orientation elsewhere. The components were uncorrelated, $r(202) = .05$, $p > .10$. In the Recovery phase, the components captured 55.1% of the variance in the original scores; non-negative vocalizations and self-comfort did not load on either component, and had low communalities (10.6% and 3.7% respectively). The first component again reflected infant negative reactivity. The second component reflected mild reactivity and orientation to the mother, with both variables loading positively, perhaps due to infants' tendency to look to their mothers to regulate distress. The components were positively correlated, $r(195) = .25$, $p < .001$.

Visual Delayed Response Task (Reznick, Morrow, Goldman, & Snyder, 2004)— This task assessed working memory using a looking rather than a reaching response to make it developmentally appropriate for 6-month-olds. On each trial, the examiner appeared at one of two windows; after the curtains are lowered, the infant's attention was directed to midline during a short delay; immediately afterward, the curtains were raised, and the direction of the infant's first look was recorded as an index of where the infant expected the examiner to reappear. The examiner then reappeared at the same location. The examiner coded infant responses during task administration, and 38% of sessions were coded independently from video to check reliability (*M* agreement = 91%); the proportion of sessions checked for reliability was higher than for other tasks because during examiner training, all sessions were double-coded. Disagreements were resolved by a third coder. The dependent measure was the proportion of correct trials for trials where the correct location switched from the previous trial, because these trials require both working memory and inhibition of a prepotent response to return to the previously reinforced location (Diamond & Doar, 1989). All infants provided usable data for this task.

Novel Object Habituation Task (Cheatham, Bauer, & Georgieff, 2006; modified from Oakes & Tellinghuisen, 1994)—In this assessment of infant attention and dishabituation to novelty, the infant was given a sample object (a colored patterned stacking ring) to explore for four 30-second-long trials. On the fifth trial, another object was substituted that differed from the sample on some dimensions (different color, texture) but not others (same global shape). On the sixth trial, the initial sample object was given again. Infant focused attention was coded from video using Observer 5.12, by research assistants who were blind to the infants' exposure status. Focused attention was coded when infants displayed a characteristic, serious facial expression, with concomitant quieting of extraneous motor activity (Ruff & Rothbart, 1996). To check reliability, 18% of sessions were coded independently (*M* agreement = 94% for orientation and 88% for attention). The dependent measure was the proportion of time infants attended to the toy in each trial. Eight infants had missing data because of fussiness ($n = 1$), examiner error ($n = 5$), and audiovisual problems ($n = 2$). Six infants had partial data because of problems with filming ($n = 2$) and early task discontinuation due to fussiness ($n = 4$).

Fagan Test of Infant Intelligence (FTII; Fagan & Shepherd, 1991)—This standardized assessment was used to index infant novelty preference and attention. It utilizes a standardized set of visual stimuli, and has been developed for administration and norm-referenced at 6 months of age. The examiner presented sets of standardized stimuli and

recorded the infant's looks to the left or right stimulus using a computer program supplied by the test developers. The test includes a series of familiarization trials, presented until the infant looked at the sample stimuli for 30 seconds, and test trials, where the familiar stimulus was presented along with a novel comparison (with presentation side balanced across trials), and the amount of time that the infant looked at both stimuli was recorded. The task yields a novelty preference score adjusted relative to normative performance at 6 months. In addition, infant attentiveness and distractibility were measured using an on-task looking index (Gaultney et al., 2005), calculated by dividing the number of looks to the sample stimuli in each familiarization trial by the total time for that trial in seconds, averaging across trials, and, for ease of interpretation, multiplying by 60 so the score reflected looks per minute. Average look length during familiarization trials was also calculated as a measure of information processing speed (Colombo, Mitchell, & Horowitz, 1988). Examiners completed a training program supplied with the FTII apparatus, and achieved reliability on the sample protocols (rs > .80, M = .92) before administering the task. Twenty-two infants did not have novelty preference scores because they did not complete the task due to fussiness (n = 17) or inattention (n = 5). On- and off-task looking indices were not calculated for eight infants who completed fewer than 50% of familiarization trials.

Birth outcomes—Information about birth outcomes (birth weight, gestational age) was collected during the neonatal phase of this study through review of participants' medical charts.

Propensity scores (PS)—PS were used to control for potentially confounding risk factors that may differ between women who do and do not smoke during pregnancy. PS reflect the estimated likelihood that a participant will smoke during pregnancy derived statistically from maternal background variables, and can be used to control for selection bias. As previously reported in detail by Fang et al. (2010), variables indexing maternal mental and physical health and demographic background were used to create the propensity scores. PS were estimated using a generalized boosted model (GBM), a non-parametric approach that is robust to situations where covariates may be non-normally distributed, their effects may be non-linear and non-additive, and multicollinearity or missing values may be present (Friedman, 2001; Imbens, 2003; McCaffrey et al., 2004). GBM was implemented using the "twang" package in R 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria). A full list of all 42 variables used in PS estimation is reported in Fang et al. (2010). The variables that contributed most strongly to PS computation (and proportion of PS variance explained) included drinking in the first month of pregnancy (14.9%), education (9.8%), drinking at the last menstrual period (8.6%), age (7.7%), IQ (6.4%), and hyperactivity (5.8%). Maternal age and education information was obtained via self-report at enrollment; women reported on drinking before and during pregnancy in a timeline follow-back interview at 14 weeks gestation; IQ was assessed using the Woodcock-Johnson Brief Intellectual Ability test (Woodcock, McGrew, & Mather, 2001); and hyperactivity was assessed using the Conners' Adult ADHD Rating Scales—Self-report: Short form (Conners, Erhardt, & Sparrow, 1998).

Other covariates—Because propensity scores model risk factors that predict maternal smoking during pregnancy, postnatal risk factors (e.g., contextual factors) cannot logically be used in their estimation. Factors that might confound the relation between PTE and infant outcomes were assessed and modeled separately.

Concurrent tobacco exposure was assessed because some studies have found correlations between ETS exposure and atypical behavioral development (Eskenazi & Castorina, 1999; Herrmann, King, & Weitzman, 2008). Mothers completed a telephone interview about their own daily smoking and their infant's exposure to ETS in the home and other contexts. The interview was conducted by a different research team member from the infant assessor, to maintain the assessor's blindness to infant exposure status. Infant ETS exposure status was coded on the basis of interview data (non-exposed = 0; exposed = 1). To provide a bioassay of ETS exposure, an infant urine sample was obtained during the lab session by placing a soft cloth in the baby's diaper. Data was missing for 41 infants because of failure to provide a urine sample (n = 23) and equipment malfunction resulting in urine sample loss (n = 18). Available urine samples were assayed for cotinine concentration, and creatinine levels were used to correct for urine concentration using the method described by Haddow, Knight, Palomaki, Neveux, and Chilmonczyk (1994). Because of concerns that mothers might underreport smoking around their infants, those infants whose mothers reported no ETS exposure but whose cotinine levels were above the 75th percentile for infants whose mothers reported ETS exposure (32.5 ng/mL) were reassigned as ETS-exposed (n = 22).

To provide an index of general developmental level, the Bayley Infant Neurodevelopmental Screener (BINS; Aylward, 1995) was administered. The BINS includes items assessing neurological intactness, receptive functions, expressive function, and cognitive processes (e.g., motor development, object permanence, imitation). The dependent measure was the normed summary score. One infant had missing data because of fussiness.

Mothers also completed the Parenting Stress Index—Short Form (PSI:SF; Abidin, 1995), a measure of parents' stress associated with the parental role, difficult temperament, and problematic parent-child relationships. The Parental Distress subscale was used as an index of mothers' parenting stress. Abidin (1995) found that this subscale was highly correlated with the Parent Domain scale of the full-length Parenting Stress Index (r = .92), and in the present sample internal consistency was high (α = .88).

Results

Statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC). Demographic information and variables measuring infants' prenatal and postnatal tobacco exposure are presented separately for prenatally tobacco-exposed (TE) and non-exposed (NE) infants in Table 1. Mothers who smoked during pregnancy were slightly but significantly younger and less educated than mothers who did not smoke. In the present sample, there was a marginal trend for TE infants to be born earlier and to weigh less at birth.

Unadjusted means for infant performance on each self-regulation measure are presented in Table 2, separately for TE and NE infants. TE and NE infants generally did not differ with

the exception of a marginal trend favoring TE infants on Visual Delayed Response performance and marginal trends for TE infants to exhibit more mild distress and avoidance behaviors during the restraint phase of the Arm Restraint task. Correlations among self-regulation measures and potential covariates were also examined (see Supplementary Table 2). Generally, correlations among measures drawn from the same task were moderate to high in magnitude and statistically significant, but correlations between tasks were small and showed no clear pattern of statistical significance.

To examine the effect of PTE on infant self-regulation, a set of hierarchical regression models were tested for each dependent measure in turn, to examine whether exposure-related differences were present after adjusting for potential confounds, whether LBW acted as a mediator, and whether effects were moderated by sex (Tabachnick & Fidell, 2007). In the first step, to control for potential confounding risk factors, PS and ETS exposure were entered into the analysis; BINS and parenting stress were not controlled because they did not differ between groups. In the second step, PTE was entered into the model to examine its effects after adjusting for confounding risks. In the third step, birth weight (centered at 2500 grams) was entered into the model as a proxy for the anoxic effects of tobacco and other toxic constituents of tobacco smoke. We tested the hypothesis that birth weight mediated PTE's effect on each self-regulation outcome by calculating the 95% confidence interval for PTE's indirect effect via birth weight, using a hierarchical Bayesian Markov chain Monte Carlo method (Biesanz, Falk, & Savalei, 2010; MacKinnon & Fairchild, 2009). In the fourth step, sex and its interaction with PTE were entered, to examine whether sex moderated the effects of PTE on self-regulation in infancy.

Hierarchical regression analyses of arm restraint component scores are summarized in Table 3. When PTE was added to the models (Step 2), it significantly predicted reactivity during the restraint phase and mild distress-mother orientation during the recovery phase, but was unrelated to orientation to the mother during the restraint phase or high distress during the recovery phase. Because component scores were standardized ($M = 0$, $SD = 1$), the unstandardized regression coefficient for PTE can be interpreted as the group difference between TE and NE infants, in *SD* units, after controlling for confounding risks: TE infants were approximately 0.5 *SD* more reactive and oriented 0.5 *SD* more to the mother relative to NE infants. When birth weight was added to the models (Step 3), it significantly predicted reactivity during the restraint phase, where 1 kg increase in birth weight was associated with a 0.4 *SD* increase in reactivity; however, because the confidence interval for PTE's indirect effect on reactivity to restraint via birth weight included 0 (*95% CI* = [−0.1152, 0.0067]), birth weight did not mediate the effect of PTE. PTE's indirect effects via birth weight were also nonsignificant for the other component scores. There was no indication that sex moderated the effect of PTE (Step 4).

Hierarchical regression analyses of delayed response and FTII measures are summarized in Table 4. For delayed response performance on reversal trials, the marginal effect of PTE favoring TE infants was no longer evident after adjusting for covariates (Step 2), there was no mediation by birth weight (*95% CI* = [−0.6989, 0.6621]) (Step 3), and effects were not moderated by sex (Step 4). For the FTII, PTE was a significant predictor of on-task looking rate and a marginal predictor of average look length after controlling for covariates: tobacco-

exposed infants showed fewer looks per minute to the familiarization stimuli and these looks tended to be shorter in duration, perhaps representing greater distractibility. For FTII novelty scores, PTE did not contribute significantly to the model. Birth weight was associated with greater novelty preference but did not act as a mediator of PTE (*95% CI* = [−0.9024, 0.0215]). PTE's indirect effects via birth weight were also nonsignificant for on-task looking rate and average look length. Sex did not significantly predict delayed response or FTII performance, or moderate the effects of PTE.

Infant attention during the Novel Object Habituation Task was analyzed using a mixed model in SAS's *Proc Mixed*. Maximum likelihood estimation permitted the inclusion of all infants who completed the majority of the task. Trial was modeled as a within-subject categorical factor with 6 levels, with an unstructured error covariance matrix. The Kenward-Rogers method was used to calculate degrees of freedom, as recommended for repeated-measures designs (Littell, Milliken, Stroup, Wolfinger, & Schabenberger, 2006). To parallel the approach taken in the hierarchical regression analyses, a series of models was tested to examine the effects of (a) confounding risks, (b) PTE, (c) birth weight, and (d) the sex-PTE interaction. The model with the lowest Bayes Information Criterion (BIC) statistic, which adjusts for parsimony and sample size, was selected as the best-fitting model (Singer & Willett, 2003). The confounding risks model was best-fitting model (*BIC* = −121.0), which included trial, PS, and ETS as predictors. The effect of Trial was significant, $F(1, 210) = 13.92$, $p < .0001$. This effect was further investigated using two planned contrasts: the first contrast (coded 4, 2, −2, −4, 0, 0) tested habituation over the four familiarization trials, and the second contrast (coded 0, 0, 0, −3, 6, −3) tested dishabituation to the novel object (Trial 5) relative to the previous familiarization trial and the final reintroduction of the familiar object. Both contrasts were statistically significant, indicating infants' levels of focused attention decreased linearly with repeated exposure to a familiar object, and increased with the introduction of a new object. The effect of PS was also significant, $F(1, 210) = 4.13$, $p < .05$. Higher maternal propensity scores were associated with less focused attention during the task. No other predictors were significantly related to focused attention or improved model fit.

Discussion

The primary goal of the present study was to examine the effects of PTE on different facets of self-regulation in 6-month-old infants, after controlling for confounding risks. This point in infant development is marked by the first signs of endogenous control of behavior, attention, and emotions. Infants whose mothers had smoked during pregnancy were more reactive during and immediately after the arm restraint procedure, a task designed to elicit frustration, and differed in looking behavior during the habituation or encoding phase of a visual novelty preference task. Other measures in the self-regulation battery did not differ as a function of PTE, including working memory/inhibitory control, novelty preference, regulation behaviors during and after arm restraint, and habituation-dishabituation during an object exploration task.

Additional goals of this study were to elucidate pathways from PTE to self-regulation by exploring the mediating effect of birth weight and the moderating effect of sex. Birth weight

was independently related to novelty preference and to reactivity during arm restraint. However, novelty preference was unrelated to PTE, and the contribution of PTE to arm restraint reactivity was virtually unchanged relative to the regression model without birth weight. Thus, we found no evidence supporting a mediating role for birth weight in PTE's effects on infant self-regulation. Furthermore, in contrast with previous evidence that boys are more vulnerable to PTE (Schuetze et al., 2008; Wakschlag & Hans, 2002; Willoughby et al., 2007), in the present study sex did not moderate any of PTE's relations with infant self-regulation outcomes.

These findings contribute to our understanding of how self-regulatory abilities develop in children whose mothers smoked during pregnancy. Many studies have found a link between PTE and behavior problems in early and middle childhood (Day, Richardson, Goldschmidt, & Cornelius, 2000; Huijbregts et al., 2008; Schmitz et al., 2006; Wakschlag & Keenan, 2001), but until recently, studies typically utilized retrospective samples and may not have adequately measured or controlled for potentially confounding risk factors. Newer studies using prospectively sampled cohorts with biochemical verification of exposure to tobacco and other substances have found substantial evidence of neonatal dysregulation (Espy et al., 2011; Mansi et al., 2007; Stroud et al., 2009). This study suggests that regulatory difficulties persist later into infancy, consistent with the small number of previous studies conducted in this age range (Schuetze, Eiden, & Coles, 2007; Schuetze et al., 2008; Willoughby et al., 2007). Furthermore, this study shows substantial effects of PTE on infant self-regulation in a sample with relatively low exposure. More work is necessary to examine how PTE affects the developmental trajectory of self-regulatory development during the transition from infancy to early childhood. There is evidence of behavioral dysregulation: in a longitudinal study, Wakschlag, Leventhal, Pine, Pickett, and Carter (2006) found that tobacco-exposed toddlers showed elevated and unchanging levels of externalizing behavior problems between 12 and 24 months, whereas their non-exposed peers showed a decrease over time. Future studies should further examine emotion regulation and attention control in this period of development, preferably with longitudinal assessments at 3 or more timepoints to permit modeling of growth trajectories (Singer & Willett, 2003).

Wakschlag and colleagues (2002) argued that PTE is associated selectively with increased risk for conduct problems. Increased reactivity coupled with poorer emotion regulation in infancy could be a marker of a developmental pathway toward later dysfunction. Early behavior could set the conditions for environmental factors that exacerbate this risk: for example, an infant who is more reactive in response to frustrating circumstances may elicit a harsher response from caregivers and other adults, creating a feedback cycle supporting continued difficulties in the emotion regulation domain. The present findings support PTE-related differences in the regulation of negative emotion in infancy, but do not provide clear evidence for the specificity of this relation, as exposure groups also differed in one measure of attention.

Propensity scores were used to adjust for confounding risk factors that differed between women who did and did not smoke during pregnancy. Inclusion of propensity scores in the regression models unmasked differences between exposed and non-exposed infants that were not otherwise apparent, as in previous work (Fang et al., 2010). The purpose of the

propensity score analysis was to correct for the influence of selection bias, and as such propensity scores cannot be interpreted directly. However, consideration of the factors that were heavily weighted in propensity score calculation might provide some insight into the nature of the confounding risk factors associated with maternal smoking during pregnancy, although their individual effects cannot be unpacked. Variables that contributed most to the propensity score calculation included several variables related to alcohol use just prior to, and very early in, pregnancy as well as maternal hyperactivity, age, IQ, and education (Fang et al., 2010). In the present study, propensity scores showed stronger relations with measures of infant attention, even when the PTE effect itself was not significant, as in the case of the novel object habituation task. ADHD and substance use disorders are highly comorbid (Wilens & Morrison, 2011), and thus it seems plausible that relations between propensity scores and infant patterns of attention could indirectly reflect genetic risk factors inherited from the mother (Thapar et al., 2003). Prenatal exposure to alcohol and other drugs is known to deleteriously affect attention skills (Gaultney et al., 2005; Streissguth et al., 1984), and although the cohort assessed in the present follow-up study was prospectively screened for high levels of alcohol use, alcohol is a potent teratogen and use even at low levels could contribute to the observed relations between propensity scores and attention-related outcomes. However, the same issues that hamper interpretation of PTE effects apply to other exposures, as genetic and environmental risk factors that influence maternal propensity to use alcohol undoubtedly also affect infant development (Handley et al., 2011).

Several limitations of the present study should inform the interpretation of its findings and guide future research. The self-regulation battery only included one task tapping infant emotional function, and was limited to response to frustration. In future studies, a broader, multidimensional approach incorporating both positive and negative emotions might facilitate assessment of infant emotional reactivity and regulation in PTE. Observational measures of infant distress in the present study reflect the contribution of both emotional reactivity and regulation, which are inherently intertwined at the behavioral level. Use of physiological measures (e.g., heart rate) would permit better separation of these factors (Stifter, Dollar, & Cipriano, 2011). Furthermore, despite our consideration of many variables that might confound the relation between PTE and infant outcomes, unmeasured covariates may still play a role. If some of the effects associated with smoking during pregnancy are actually caused by underlying risk factors (e.g., if exposure groups differ because of genetic risk factors that contribute to maternal smoking during pregnancy), PTE would be best interpreted as a marker of an at-risk developmental trajectory rather than as the cause of developmental insult. Research using genetically informed designs coupled with in-depth measurement of behavior is needed to distinguish between these alternatives. However, the implications for targeted intervention are similar in either case. Finally, it is important to consider the generalizability of this study's findings. The initial cohort was recruited targeting women with demographic characteristics associated with smoking during pregnancy, yielding a sample at relatively high sociodemographic risk; the present follow-up study was generally successful at retaining eligible participants, but less educated and minority women were more likely to be lost to follow-up. As such, the results of this study are generalizable to populations relatively high in sociodemographic risk, but may be less applicable to those most at risk.

The present study has a number of unique strengths. This follow-up study utilized a prospective cohort with multi-method assessment of prenatal and postnatal exposure to tobacco. Confounding risk factors were statistically controlled using propensity scores, a method with demonstrated utility to disentangle the effects of PTE from other confounding risk factors. Self-regulation was assessed directly in the lab setting, using measures of infant control of attention, memory, and emotions. The results of this study indicate that, midway through the first year, infants who were exposed to tobacco smoke during pregnancy differ from non-exposed infants in emotional reactivity and control of attention during encoding. Future follow-ups of this cohort are underway to examine how infant functioning relates to outcomes in early childhood, when self-regulation is more developed and deficits have clear consequences for academic and social functioning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Descriptive statistics for tobacco exposure, and birth outcomes, by prenatal tobacco exposure group.

Measure	TE (*n* = 127)		NE (*n* = 91)	
	M	*SD*	*M*	*SD*
Infant sex (% female)	48.0	--	47.3	--
Birth weight (g) +	3374.3	455.6	3485	436.5
Gestational age (weeks) +	39.0	1.07	39.3	1.13
Age at 6-month assessment, corrected for prematurity (weeks)	25.8	1.05	25.7	0.93
Maternal age at delivery (years) *	25.4	5.02	26.9	4.88
Maternal education (years) *	12.9	1.35	13.8	1.65
Propensity score (estimated propensity to smoke during pregnancy; 0–1)***	0.74	0.207	0.27	0.167
Self-reported smoking (cigarettes/day):				
First trimester ***	5.3 (*n* = 120)	5.70	0	0
Second trimester ***	3.8 (*n* = 120)	6.30	0	0
Third trimester ***	3.4 (*n* = 120)	6.13	0	0
At 6 months ***	9.6	24.47	0.1	0.52
Parenting stress at 6 months (percentile)	47.1	32.53	47.8	30.84
BINS (raw score; 0–13)	10.2	1.62	10.0	1.70

Note.

+ $p < .10$;

* $p < .05$;

*** $p < .001$;

BINS = Bayley Infant Neurodevelopmental Screener; NE = non-exposed; TE = tobacco-exposed

Table 2

Descriptive statistics for infant regulation of attention and memory, by prenatal tobacco exposure group.

Task/Questionnaire		**TE (*n* = 115–127)**		**NE (*n* = 82–91)**	
Dependent measure (range)	**Range**	***M***	***SD***	***M***	***SD***
Arm Restraint: Restraint Phase					
High Distress component score	−1.49–1.93	0.10	0.980	−0.12	1.018
Mother Orientation component score	−2.10–3.66	0.03	1.142	−0.04	0.783
Arm Restraint: Recovery Phase					
High Distress component score	−1.62–1.84	0.00	0.985	0.00	1.03
Mild Distress/Mother Orientation component score	−1.47–3.93	0.05	1.015	−0.07	0.980
Visual Delayed Response reversal trial performance (%) +	14–100	59.4	15.93	55.0	17.22
Novel Object Habituation Task (% sustained attention)					
Familiarization Trial 1	0–97.5	48.4	24.26	49.4	26.12
Familiarization Trial 2	0–100	42.8	25.75	44.9	26.91
Familiarization Trial 3	0–100	40.7	27.82	44.4	28.05
Familiarization Trial 4	0–98.1	37.2	25.83	40.7	26.53
Novel Test Trial 5	0–100	46.0	27.96	49.0	25.17
Familiar Test Trial 6	0–100	34.4	24.45	37.2	26.82
Fagan Test of Infant Intelligence					
Adjusted novelty score (% looking to novel)	40.5–88.7	59.0	6.77	58.5	8.09
On-task looking rate (# on-task looks per minute)	5.6–44.1	19.3	6.31	19.3	6.09
Average look length (seconds) +	0.66–2.46	1.22	0.315	1.30	0.375

Note.

+ $p < .10$;

NE = non-exposed; TE = tobacco-exposed

Table 3

Hierarchical regression analyses of Arm Restraint component scores for Restraint phase (n = 202) and Recovery phase (n = 195)

	Restraint Phase: Reactivity			Restraint Phase: Mother Orientation			Recovery Phase: High Distress			Recovery Phase: Mild Distress/Mother Orientation		
	***b* (SE)**	**β**	**ΔR^2**	***b* (SE)**	**β**	**ΔR^2**	***b* (SE)**	**β**	**ΔR^2**	***b* (SE)**	**β**	**ΔR^2**
Step 1			.003			0.014			0.001			0.011
Intercept	−0.05 (.147)	0		−0.13 (0.146)	0		0.03 (0.15)	0		0.09 (0.151)	0	
PS	0.15 (.236)	0.05		0.12 (0.235)	0.04		−0.02 (0.242)	−0.01		−0.26 (0.241)	−0.08	
ETS	−0.08 (.157)	−0.02		0.24 (0.156)	0.11		−0.05 (0.161)	−0.02		0.180 (0.161)	0.08	
Step 2			.017^{+}			0.000			0.000			0.028*
Intercept	0.004 (0.150)*	0		−0.14 (0.150)	0		0.03 (0.156)	0		0.16 (0.153)	0	
PS	−0.46 (.371)	−0.13		0.18 (0.371)	0.05		−0.10 (0.379)	−0.03		−0.94 (0.372)*	−0.28	
ETS	−0.11 (.158)	−0.05		0.25 (0.159)	0.11		−0.06 (0.165)	−0.03		0.11 (0.161)	0.05	
PTE	0.48 (.230)*	0.24		−0.05 (0.227)	−0.02		0.07 (0.232)	0.03		0.54 (0.228)*	0.27	
Step 3			.014*			0.001			0.002			0.000
Intercept	−0.36 (0.207)	0		−0.19 (0.211)	0		−0.06 (0.216)	0		0.20 (0.212)	0	
PS	−0.46 (0.366)	−0.14		0.17 (0.373)	0.05		−0.12 (0.381)	−0.04		−0.93 (0.374)*	−0.28	
ETS	−0.13 (0.156)	−0.06		0.25 (0.159)	0.11		−0.06 (0.165)	−0.03		0.11 (0.162)	0.05	
PTE	0.50 (0.226)*	0.25		−0.04 (0.230)	−0.02		0.08 (0.234)	0.04		0.53 (0.230)*	0.6	
BW	0.39 (0.156)*	0.17		0.06 (0.159)	0.02		0.10 (0.162)	0.04		−0.04 (0.16)	−0.02	
Step 4			.011			0.005			0.012			0.004
Intercept	−0.47 (0.235)*	0		−0.19 (0.240)	0		−0.09 (0.244)	0		0.11 (0.240)	0	
PS	−0.49 (0.367)	−0.15		0.17 (0.375)	0.05		−0.12 (0.382)	−0.04		−0.96 (0.376)*	−0.29	
ETS	−0.14 (0.157)	−0.06		0.23 (0.160)	0.11		−0.08 (0.165)	−0.03		0.12 (0.163)	0.05	
PTE	0.73 (0.276)**	0.36		0.04 (0.282)	0.02		0.24 (0.288)	0.12		0.63 (0.284)*	0.31	
BW	0.42 (0.158)**	0.19		0.08 (0.161)	0.04		0.14 (0.164)	0.06		−0.04 (0.161)	−0.02	
Sex	0.17 (0.211)	0.08		−0.04 (0.216)	−0.02		0.00 (0.223)	0.00		0.20 (0.220)	0.10	
Sex X PTE	−0.41 (0.282)	−0.19		−0.15 (0.288)	−0.07		−0.29 (0.294)	−0.13		−0.16 (0.290)	−0.08	

Note.

+ $p < .10$,

* $p < .05$,

** $p < .01$;

BW = birth weight; ETS = environmental tobacco smoke; PS = propensity score; PTE = prenatal tobacco exposure.

Table 4

Hierarchical regression analyses of Delayed Response reversal trial percentage correct (n = 218), FTII novelty score (n = 197), and FTII on-task looking rate and average look length (n = 211).

	Delayed Response			FTII Novelty Score			FTII On-task Looking Rate			FTII Average Look Length		
	***b* (SE)**	**β**	**ΔR^2**	***b* (SE)**	**β**	**ΔR^2**	***b* (SE)**	**β**	**ΔR^2**	***b* (SE)**	**β**	**ΔR^2**
Step 1			0.007			0.009			0.027^{+}			0.004
Intercept	$55.0\ (2.37)^{**}$	0		$57.7\ (1.12)^{**}$	0		$17.5\ (0.89)^{**}$	0		$1.3\ (0.05)^{**}$	0	
PS	4.2 (3.76)	0.08		2.2 (1.76)	0.09		$2.6\ (1.41)^{+}$	0.13		−0.1 (0.08)	−0.06	
ETS	0.9 (2.48)	0.03		−0.6 (1.15)	−0.04		1.2 (0.93)	0.09		0.0 (0.05)	0.02	
Step 2			0.012			0.003			0.039^{**}			0.014^{+}
Intercept	$55.8\ (2.41)^{**}$	0		$57.6\ (1.14)^{**}$	0		$17.0\ (0.89)^{**}$	0		$1.3\ (0.05)^{**}$	0	
PS	−3.1 (5.91)	−0.06		3.8 (2.75)	0.15		$7.5\ (2.18)^{**}$	0.37		0.1 (0.12)	0.09	
ETS	0.2 (2.51)	0.00		−0.4 (1.17)	−0.03		$1.7\ (0.93)^{+}$	0.13		0.0 (0.05)	0.04	
PTE	5.9 (3.66)	0.18		−1.2 (1.69)	−0.09		$-4.0\ (1.35)^{**}$	−0.32		$-0.1\ (0.08)^{+}$	−0.19	
Step 3			0.000			0.026^{*}			0.000			0.000
Intercept	$55.7\ (3.39)^{**}$	0		$55.0\ (1.57)^{**}$	0		$17.1\ (1.24)^{**}$	0		$1.3\ (0.07)^{**}$		
PS	−3.2 (5.94)	−0.06		3.1 (2.73)	0.13		$7.6\ (2.20)^{**}$	0.37		0.1 (0.13)		
ETS	0.2 (2.52)	0.00		−0.4 (1.16)	−0.02		$1.7\ (0.93)^{+}$	0.13		0.0 (0.05)		
PTE	5.9 (3.70)	0.18		−0.6 (1.70)	−0.04		$-4.0\ (1.37)^{**}$	−0.32		$-0.1\ (0.08)^{+}$		
BW	0.1 (2.54)	0.00		$2.6\ (1.16)^{*}$	0.16		−0.2 (0.93)	−0.01		0.0 (0.05)		
Step 4			0.002			0.001			0.005			0.012
Intercept	$56.6\ (3.88)^{**}$	0		$55.4\ (1.82)^{**}$	0		$16.5\ (1.42)^{**}$	0		$1.3\ (0.08)^{**}$	0	
PS	−3.1 (5.97)	−0.06		3.2 (2.75)	0.13		$7.5\ (2.20)^{**}$	0.37		0.1 (0.13)	0.09	
ETS	0.2 (2.54)	0.01		−0.4 (1.17)	−0.02		$1.7\ (0.94)^{+}$	0.13		0.0 (0.05)	0.03	
PTE	4.2 (4.50)	0.13		−1.1 (2.09)	−0.07		$-3.0\ (1.66)^{+}$	−0.24		−0.1 (0.09)	−0.21	
BW	−0.1 (2.57)	0.00		$2.6\ (1.19)^{*}$	0.16		−0.1 (0.94)	−0.01		0.0 (0.05)	0.01	

	Delayed Response			FTII Novelty Score			FTII On-task Looking Rate			FTII Average Look Length		
	***b* (SE)**	**β**	**ΔR^2**	***b* (SE)**	**β**	**ΔR^2**	***b* (SE)**	**β**	**ΔR^2**	***b* (SE)**	**β**	**ΔR^2**
Sex	−1.3 (3.51)	−0.04		−0.5 (1.69)	−0.03		1.0 (1.29)	0.08		−0.1 (0.07)	−0.12	
Sex X PTE	3.1 (4.60)	0.09		0.8 (2.13)	0.05		−1.7 (1.69)	0.13		0.0 (0.10)	0.02	

Note.

$^{+}$ p < .10,

* p < .05,

** p < .01;

BW = birth weight; ETS = environmental tobacco smoke; FTII = Fagan Test of Infant Intelligence; PS = propensity score; PTE = prenatal tobacco exposure.