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The Impact of Maternal Smoking on Fast Auditory Brainstem Responses

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Abstract

Deficits in auditory processing have been posited as one of the underlying neurodevelopmental consequences of maternal smoking during pregnancy that leads to later language and reading deficits. Fast auditory brainstem responses were used to assess differences in the sensory processing of auditory stimuli among infants with varying degrees of prenatal cigarette exposure. Maternal report of consumption of cigarettes and blood samples were collected in the hospital to assess exposure levels and participants were then seen at 6-months. To participate in the study, all infants had to pass the newborn hearing exam or a clinically administered ABR and have no known health problems. After controlling for participant age, maternal smoking during pregnancy was negatively related to latency of auditory brainstem responses. Of several potential covariates, only perinatal complications and maternal alcohol use were also related to latency of the ABR responses and maternal smoking level accounted for significant unique variance after controlling for these factors. These results suggest that the relationship between maternal smoking may lead to disruption in the sensory encoding of auditory stimuli.

Keywords

Maternal smoking; ABER; language development; infants

1. Introduction

Although smoking in pregnancy is discouraged by the medical community and the overall acceptance of smoking has declined in American culture [1], a significant number of pregnant women continue to smoke. The National Health Interview Survey reported that smoking among females ranged from a high of 33.9% in 1965 to a low of 17% in 2007 and estimates of the prevalence of women of childbearing age who are smokers has ranged from 19–25% over the last decade [2–5]. Although it is fairly common for women to reduce their tobacco use during pregnancy, the majority continue to smoke throughout the pregnancy [6–8]. In 2002, 11.4% of all mothers reported smoking during pregnancy on birth certificates [9] but this is most likely an underestimate of actual use.

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Aspects of the teratogenic impact of maternal smoking during pregnancy have been investigated for over 50 years with reduction in birth weight [10,11] being a consistent finding since the original observation in 1957 [12]. Other negative perinatal outcomes, including increased risks of spontaneous abortion [13], prematurity [14], oral clefting [15], neonatal death [13], and Sudden Infant Death Syndrome [16,17], also have been observed among the children of smokers. Various aspects of cognitive and behavioral problems associated with prenatal exposure have been noted as well [18–30].

Among the neurocognitive outcomes examined, the most consistent findings have been disturbances in aspects of auditory functioning. These disturbances have been reported by several investigators employing different methodologies from the fetal period through later childhood and into adulthood. Fetuses of smokers have been found to be less responsive than a contrast group to maternal speech [31] and impairments in neonatal auditory habituation on the Brazelton Neonatal Behavioral Assessment Scale [32] has been reported repeatedly (e.g., [33–35]). Using polygraphic studies of sleep, Franco et al. [36] found that infants of smokers showed decreased arousal to auditory stimuli both as newborns and as 12-week-olds.

By 6-months of age, infants exposed prenatally to tobacco smoke demonstrated poorer cardiac orienting responses to auditory stimuli while performing comparably to a reference group when exposed to visual stimuli [37]. In the Ottawa Prenatal Prospective Study (OPPS), at 12 and 24 months, tobacco-related differences were found [38] on an auditory cluster derived from the Infant Behavior Record of the Bayley Scales of Infant Development (BSID[39]). When these children were four to seven years of age, deficits in performance on auditory, but not visual, vigilance tasks were found [40] and, among 6-to 11-year- olds, poorer performance on a central auditory processing task was found [41], suggesting that observed early deficits in auditory processing persisted into middle childhood. Fried and his colleagues have posited that deficits in auditory functioning found in the infants in his prospective longitudinal cohort of tobacco-exposed children were linked to the language and reading difficulties [34,42–46] that persisted into adulthood [47]. In different samples that provide converging evidence regarding an underlying auditory deficit in children of smokers, prelinguistic skills in 6-month-olds [37] and vocalization of vowel-consonant combinations in 8-month-olds [48] were delayed in children of women who smoked in pregnancy. Among a sample of preschoolers, vocabulary expression [49] was lower among children whose mothers smoked.

The mechanisms of action of nicotine on the auditory pathway have been investigated as a potential basis for the relationship between maternal smoking and impairments to auditory and language functioning. The auditory pathway is heavily mediated by cholinergic molecules, particularly acetylcholine (ACh), a neurotransmitter that activates receptors that are also responsive to nicotine. These receptors, referred to as nicotinic acetylcholine receptors (nAChRs; [50]), can be altered by chronic exposure to nicotine, particularly if the exposure is very early in development, as nicotine can mimic the stimulation of ACh on these receptors in the ascending auditory pathways. Among adult animals exposed to nicotine, decreased latency to auditory stimulation has been found in central auditory evoked responses, suggesting that nicotine serves to prime the nicotinic receptors for faster responding [51–54]. A similar facilitation of response has been found in adult human smokers using fast and middle latency auditory evoked responses [55–57]. Nicotine exposure early in development has also been found to have long-term effects on ACh activation. In an animal model, rat pups exposed to chronic nicotine activation showed a decreased latency in stimulus detection as well as alterations in responsiveness of ACh pathways in the cerebral cortex and poorer performance on an auditory-cued active avoidance task [53]. This alteration in the manner in which auditory stimuli are processed by the sensory system may be linked to the auditory deficits seen in children whose mothers smoked during pregnancy.

Auditory brainstem evoked responses (ABERs) reflect the initial encoding of auditory and verbal stimuli in that they are the neurophysiological responses that are triggered along the auditory pathway in response to sound waves [58]. This process starts with an action potential conducted along the eighth nerve, moving to the brainstem, and finally to the auditory cortex. The electrical signals produced as the action potential travels along this pathway result in characteristic waveforms known as the auditory brainstem evoked response. Electrical waveforms that occur between 2 and 12 msec after stimulation are known as fast auditory responses or the Jewett Sequence [59,60] and are used to assess peripheral sensory encoding. Such responses are known to be altered by various teratogens [61,62] and certain genetic abnormalities [63]. In addition, reduced latencies have been found in children with phonemic language and reading deficits [64,65], suggesting that responses that occur too quickly may be disruptive to the encoding of the subtle phonemic characteristics of speech.

Accordingly, we investigated the relationship between fast auditory brainstem responses in children whose mothers smoked at several levels during pregnancy while controlling for other factors associated with maternal smoking that may impact child development. These factors included differences in environmental and maternal lifestyle variables, including other drug use, which may impact the development of the auditory system. We hypothesized that there is a significant dose-response relationship between maternal smoking and latencies of auditory brainstem evoked responses such that higher levels of maternal smoking are associated with reduced levels of response latency.

2. Methods

2.1 Participants

The initial pool of participants included 351 women and their infants who were recruited following delivery from two hospitals in the Atlanta metropolitan area and agreed to participate in a two year longitudinal study of infant language development. Recruitment was based on a stratified dose-response sampling procedure using the mothers' self-report of cigarettes smoked per day to obtain better representation of the women who smoke at higher dosage levels. While effects have been observed at lower levels of exposure, it is well known from the study of other teratogenic exposures (i.e. alcohol) that it is necessary to include the higher doses to establish the full range of outcomes (Vorhees, 1986). As such, we opted to recruit women who smoked within three groups: less than ½ pack of cigarettes a day (<10 cigarettes), between ½ pack and 1 pack a day (10–19 cigarettes), and a pack or more a day (≥20). Non-smokers were chosen based on their similarity to the overall pool of smokers on age and race. Parameters of socio-economic status (i.e. child's medicaid status) were also used to select between multiple non-smokers who met the age and race criteria but this was not always possible.

Two hundred and thirty five of these participants returned for the 6-month follow up visit. Auditory brainstem evoked responses (ABER) were successfully obtained from 172 of the infants at 6 months. ABERS were not obtained on the remaining 63 participants because the infants did not fall asleep during their 6-month visit, would not tolerate the leads being placed on them, or produced traces that were not readable.

2.2 Hospital Recruitment and Procedures

Recruiters visited the hospitals' postpartum units several times per week to screen for potential participants. Women, at least 24 hours postpartum, were approached and if they were interested, a short screening questionnaire was administered to determine eligibility. Women were eligible if they were at least 18 years of age and the primary language in the home was English. The latter criterion was used for inclusion because the primary focus of the study was the impact of maternal cigarette smoking in pregnancy on phonemic awareness, which

undergoes significantly different developmental processes for children who are bilingual [66]. Infants had to be a singleton and at least 34 weeks gestational age with no known medical conditions that might independently affect developmental and language outcomes (e.g. genetic disorders, severe complications of prematurity, intraventricular hemorrhage Grades III and IV, perinatal trauma, visual or hearing impairments). To be eligible for enrollment, infants also had to pass the otoacoustic emission (OAE) testing conducted routinely in the hospitals as part of a newborn hearing screening program mandated by Georgia law or a clinically administered ABR if they failed the OAE.

Mothers completed an informed consent procedure approved by the Institutional Review Boards of the School of Medicine and the Hospitals. This procedure was consistent with the provisions of the Health Insurance Portability and Accountability Act of 2001. During the same visit, a maternal interview was completed about prenatal care, tobacco, alcohol, and other drug use in the three months prior to conception and during each trimester of pregnancy. For cigarette use, mothers were asked how many cigarettes per day they smoked prior to pregnancy and during each trimester. Alcohol consumption was broken down into beer, wine, and liquor. Participants were asked to describe the pattern and quantity of drinking for each type of alcohol substance. The average ounces of absolute alcohol per week (AA oz/wk) was then calculated using the quantity-frequency-variability interview technique [67]. To assess for other prenatal exposures, mothers were asked whether they had ever used a series of drugs; if so, they were asked whether they used each one during pregnancy (Drug Grid, [68]). Medical information and information about tobacco and other drug use was also obtained through abstraction of mother and infant medical records. Mothers were asked to provide a blood sample, which was collected by the nursing staff of the hospital, to assess cotinine levels, a biochemical marker of nicotine that has a longer half-life than nicotine (18 vs. 2 hours), and a urine sample to assess for exposure to illicit drugs. Women were excluded from participation if the urine screen was positive for cocaine or opiates. As compensation for their time, women were paid $50 and given a small toy and t-shirt for the infant.

Group status was determined by computing the average number of cigarettes consumed across the three months prior to pregnancy and each of the three trimesters. Five women reported smoking cigarillos in the periconceptual period. Each cigarillo was equated to five cigarettes for computing average number of cigarettes per day. The *Light* group (n = 42) smoked an average of less than 10 cigarettes per day; the *Moderate* group (n = 58) smoked an average between 10 and 19 cigarettes; and the *Heavy* group (n=15) smoked an average of 20 or more cigarettes per day.

Comparisons of verbal reports of smoking behavior and cotinine results were made to validate group status as well. Smokers (n=4) who reported quitting by the third trimester but who had cotinine levels consistent with an active smoking status were assigned the mean level of cigarettes per day for their grouping category based on their report of smoking at the 6-month interview or their pre-pregnancy report of consumption if they denied smoking in the third trimester at the 6-month interview as well. One woman who reported being a nonsmoker had cotinine levels consistent with active smoking. She was recategorized as a smoker and assigned a smoking level based on the mean level of cigarettes per day that she reported at the 6-month interview at which time she acknowledged smoking during pregnancy.

2.3 Six Month Assessment Procedures

Mothers and infants were seen again at the University laboratory for assessment at 6 months. During their visit, a brief medical interview and screening were conducted. Infants were screened by the study nurse for active ear infections, recent placement of myringotomy tubes, or other current illnesses. A maternal interview questionnaire was repeated to update information obtained from the hospital interview. Mothers were asked to report retrospectively

about their tobacco and other drug use and to report their current use. The visit to the laboratory lasted approximately 2–3 hours. Mothers were offered childcare, transportation or reimbursement for fuel, as well as $50 in cash as compensation for their time.

2.3.1 Mother and Family Measures—In addition to the impact of prenatal tobacco smoke exposure on auditory development, there are associated environmental factors that may mediate the relationship between cigarette exposure and later neurodevelopmental outcomes. In most studies, mothers who use cigarettes while pregnant differ in many ways from mothers who do not, including having lower socio-economic status, more psychopathology and an increased use of other substances, including alcohol and marijuana [69].

To measure these factors, mothers were asked to complete a questionnaire assessing their socio-economic status and demographic characteristics; the Drug Grid [68], which is a measure of current and past substance use; the Symptom Checklist 90-R (SCL90R: [70]), which assesses maternal psychopathology; and the Structured Clinical Interview [71], which assesses family structure and consistency in caregiving, child protective services involvement, and child's emotional adjustment. Finally, mothers were asked to provide urine samples to analyze for the presence of metabolites of nicotine (cotinine) and for cocaine, marijuana, and other drugs.

2.3.2 Infant Measures—At the 6-month follow-up, auditory brainstem responses were collected while the infants slept, typically at the end of their visit to the laboratory. Testing was done in a secluded room with dim lighting by the infant tester or a research nurse who were kept blind to the infant's group status. Biopac's STM100C stimulator was used to repetitively produce a.08 msec click in a pediatric tubephone placed into the infant's ear at 88 dB SPL (sound pressure level). Electrodes were placed on the ipsilateral earlobe (−), the contralateral earlobe (ground), and the forehead (+) to assess the evoked response to the stimulation. One thousand fast auditory brainstem responses were collected and averaged using a MP100 System and the AcqKnowledge software from Biopac (see Biopac #AS105 [72]). Amplification by the ERS100A amplifier was set at 5,000 with a bandpass filter of 60 to 5000 Hz. Electrode impedances ranged from 1 to 10 Kohm. Latency and amplitudes of Waves 1, 3, and 5 were then read from the averaged brainstem responses. These peaks were selected as they are the most common and easily detectable from the evoked response to the stimulation [73]. Wave 1 was defined as the first peak in the trace following 1.3 msec. Wave 3 was defined as the first peak in the trace following 3.0 msec. Wave 5 was defined as the first peak in the trace following 5.5 msec. Once the respective peak was defined, the latency of the peak from stimulus onset was determined using the AcqKnowledge software.

The infants were also given the Bayley Scales of Infant Development, 2nd Edition (BSID-II [71]) to assess neurodevelopmental functioning with standard scores (x=100, std=15) that assess mental or cognitive development the Mental Developmental Index (MDI), and motor development, the Psychomotor Developmental Index (PDI). Examiners were psychologists or practicum or post-doctoral trainees who were blind to group status.

A urine sample (approximately 5 cc) was collected from the infants during their visit to the laboratory using pediatric urine collection bags to assess for cotinine levels to measure their on-going, passive exposure to environmental tobacco smoke.

3. Results

Group differences on measures were evaluated in two steps. First, dosage group was defined categorically in either univariate or multivariate analysis of variance and post-hoc comparisons were made to determine the nature of the group differences. Second, in order to evaluate dose-response relationships, planned polynomial contrasts were conducted to evaluate the response

surface between dosage group and outcomes for linear, quadratic, and cubic relationships. None of the quadratic and cubic relationships were significant for the outcome measures so only linear relationships are presented. To further examine dose-response-relationships between indices of maternal smoking using continuous scaling and outcomes, simple Pearson correlations were computed between number of cigarettes smoked per day reported for the 3-months prior to pregnancy, each of the trimesters, the overall average of the perinatal period, and the pre- and post- levels of cotinine obtained from biosamples collected from the mother and infant.

3.1 Attrition Analysis

Comparisons of those seen at 6-months and those not seen at 6-months resulted in no differences in demographic characteristics, prenatal care and vitamin usage, or neonatal status variables. The groups differed in only one medical characteristic, the number of previous miscarriages, which was significantly higher ($F(1, 345) = 15.17$, $p < .000$) in those who failed to attend the 6-month follow-up as compared to those who were seen at 6-months. The groups differed in two areas related to the reporting of their substance use. Those seen at 6-months reported significantly higher levels of weekly absolute ounces of alcohol (AA oz/wk) in each of the perinatal periods in comparison to those not seen at 6-months (3-months prior ($F(1,343) = 5.73$, $p < .02$); 1st trimester ($F(1, 343) = 6.14$, $p < .01$; 2nd trimester ($F(1, 343) = 7.83$, $p < .005$); and 3rd trimester $F(1,342) = 7.48$, $p < .007$). In contrast, those seen at 6-months reported smoking significantly fewer cigarettes ($F(1,345) = 8.16$, $p < .005$; Seen: X=11.58, STD= 10.7) per day prior to pregnancy than those who failed to attend the six-month follow-up (Not Seen: X=15.32, STD=12.73) but the groups did not differ on self-reported cigarette use during pregnancy or in group assignment.

Analysis of cotinine levels were conducted using a log transformation of the cotinine value as a result of the extreme ranges in the sample but are reported in terms of mean cotinine level. Mothers who did not attend the 6-month follow-up had significantly higher levels of cotinine (log transformation of cotinine value $F(1, 226) = 6.30$, $p < .013$; Mean cotinine value=26.31, STD=46.23) at birth than the mothers of the children who were seen at 6-months (Mean cotinine value=16.88, STD=49.00).

Comparisons of those who were seen at 6-months and for whom an ABER was obtained to those for whom one was not obtained also yielded a group difference. The groups did not differ on any demographic measures, neonatal status variables, prenatal care or vitamin usage variables, or infant developmental status at 6-months. Group difference was found in the log values of maternal birth cotinine levels. Infants for whom an ABER was obtained had significantly lower maternal birth cotinine levels than those for whom a sample was not obtained (log transformation of cotinine value $F(1, 151) = 4.65$, $p < .033$; ABER Obtained: Mean cotinine value=35.18, STD=74.7 vs. ABER Not Obtained: Mean cotinine value=9.50, STD=31.1). Otherwise, the groups did not differ in self-reported use of cigarettes per day in any of the periconceptual periods sampled or in self-report of any other substances.

3.2 Group Characteristics of ABER Sample

Parental characteristics by group status are presented in Table 1. Characteristics were analyzed for group differences and linear trends across groups are indicated using asterisks. Groups did not differ on parental age or race but differed in marital status, parental education, income level, insurance type and parity. Infants of mothers who did not smoke were more likely to have parents that were married, have higher education levels, and greater income than the families of infants whose mothers smoked in pregnancy and these relationships were linearly related to dosage level. Maternal smoking level was also positively linked to number of previous offspring.

Child characteristics by group status are presented in Table 2 with group means presented in columns and linear trends across groups denoted using asterisks. As expected, linear dose-response relationships were found between group status and two parameters of birth size: birthweight and length. The groups did not differ in head circumference, gender, prematurity status or one minute Apgar scores. Five minute Apgar scores did vary by group ($F(3,165) = 4.63$, $p < .05$). Post hoc comparisons indicated that the moderate exposure group had higher scores than did the light exposure group. There also was a group difference in gestational age ($F(3,165) = 4.63$, $p < .05$) but post hoc comparisons resulted in only a trend ($p < .06$) for the moderate group having lower gestational age than did the control group. No differences were found in the infants' adjusted age for their 6-month visit or in their developmental status, using the Mental and Psychomotor Developmental Index scores from the BSID-2.

Reported cigarette usage by trimester and group status is in Table 3. Significant linear dose response relationships were found for group level for each of the assessment periods (3-months prior to pregnancy and each trimester of pregnancy). A linear dose-response relationship was also obtained on maternal blood cotinine levels obtained at birth. Table 4 displays the correlations between self-report measures of consumption and cotinine levels of the mother and infant.

Consumption of caffeinated beverages, including coffee ($F(1, 168) = 16.7$, $p < .000$), tea ($F(1, 168) = 6.4$, $p < .012$), and sodas ($F(1, 167) = 18.5$) increased as maternal smoking level increased. Maternal smoking level was also positively associated with the number of days of binge drinking (> 5 drinks) in pregnancy ($F(1, 166) = 4.1$, $p < .045$) but was not related to absolute ounces of alcohol intake reported during pregnancy. Usage of marijuana was positively associated with maternal smoking level ($F(1, 162) = 7.12$, $p < .008$). None of the nonsmokers reported using marijuana during pregnancy but 12.5% of the light, 14.5% of the moderate, and 14.3% of the heavy dose group reported using marijuana at some point in their pregnancy.

3.3 ABER Results

In a repeated measures analysis of variance controlling for infant age in days, maternal smoking level was negatively related to response latency ($F(3, 150) = 3.4$, $p < .019$, linear contrast $p < .006$). Only a trend was found for a wave* group interaction ($F(6, 300) = 1.7$, $p < .12$, linear contrast $p < .061$). Table 5 shows average wave latencies by cigarette exposure group and the results of separate ANOVAs conducted on each wave form, including the linear contrast of dose-response relationships among groups. This analysis was done to complement the repeated measures analysis as a result of the loss of some participant data (n=17) in the repeated measures analysis associated with not having valid estimates of each wave latency. A significant negative linear relationship was found on Wave 5 latency ($t(1,169) = -3.25$, $p < .001$) and trends for similar relationships were found on Wave 1 ($t(1, 154) = -1.53$, $p < .128$) and 3 ($t(1,165) = -1.69$, $p < .093$). The interval between Wave 5 and Wave 1, the V-I latency, has historically been used to assess neural conduction along the brainstem and has been used as an index of neural maturation [59]. V-I latencies were computed and analyzed as well. After adjusting for the age of assessment, a significant negative linear relationship was found ($t(1,154) = -2.76$, $p < .007$) between V-I latency and maternal smoking level.

Latencies of each wave were also related to the average number of cigarettes consumed, cigarette use by trimester, and cotinine level obtained at birth after adjusting for the child's age at the time of the assessment. The results are in Table 6. The latency on Wave 5 was negatively related to the overall average number of cigarettes consumed over the periconceptual period and each of the three month intervals sampled. Wave 3 latency was negatively related to the overall average number of cigarettes and cigarette use in the 3-months prior to pregnancy. Trends were found for relationships between Wave 3 latency and 1st and 2nd trimester cigarette use per day. For Wave 1, the latency was negatively related to cigarette use in the third trimester

and to the log of the cotinine value obtained at birth from the maternal blood sample. Trends were also found for overall average number of cigarettes per day and 2nd trimester use. The V-I latency was negatively related to overall average number of cigarettes consumed and cigarette use prior to pregnancy and use in the first trimester. A trend was found for a negative linear relationship between V-I latency and 2nd trimester cigarette use.

There were no significant relationships between latencies of the waves and postnatal urinary cotinine values of the infant obtained at the 6-month visit. A significant negative linear relationship between mother's urinary cotinine value at 6-months and Wave 5 latency was found (r= −.182) and V-I latency (r=−.186). However, these relationships were no longer significant after accounting for the average number of cigarettes used during pregnancy, suggesting that mother's postnatal cigarette consumption was not adding unique variance to the prediction of Wave 5 or V-I latencies. The same can be said for reversing the order of prediction: after entering mother's postnatal urinary cotinine, prenatal cigarette usage was no longer significantly related to the outcomes.

Additional analyses were then conducted to assess the relative contribution of maternal cigarette use after controlling for potentially confounding demographic and lifestyle factors observed in the sample. In order to carry out this analysis, the data had to be formatted for regression analysis. This involved reducing the independent variables (three wave latencies) into one variable reflecting the shared variance among the wave latencies and reducing the numerous potential covariates collected as part of the study into a limited number of constructs. Potential covariates were categorized as being socio-environmental variables, pregnancy care and complications, infant health status, maternal psychopathology, and other substance use. Factor analyses using a principal components procedure with a varimax rotation were used for data reduction. Factor loadings for all included variables were standardized to z-scores and outputted for future analysis.

3.3.1 Wave Latency Factor—As the repeated measures analysis of variance resulted in an overall group effect, the shared variance of the three wave forms was the primary outcome. A factor reflecting the shared variance in the latencies of the three waves was derived from a principal component factor analysis. The factor that emerged had an eigen value= 1.7 and accounted for 56.4% of the shared variance between latencies. Correlations with the wave factor for each of the waves were as follows: Wave 1 (.703), Wave 3 (.791), and Wave 5 (.761).

3.3.2 Socio-environmental Variables—Of the 12 variables entered from the domain of family background variables and socio-environmental status, four factors emerged. The first factor (SES-factor) had an eigen value of 4.1 and accounted for 34.5% of the variance. This factor was positively related to parental education, household income, and parental age and negatively related to receiving public assistance (AFDC and Medicaid) and WIC services. The second factor (eigen value 1.8, 15.1% of the variance) loaded positively on maternal working and number of work hours (Mom working-factor). The third factor (eigen value 1.4, 11.9% of the variance) loaded positively on parental age and number of children (Family maturity-factor). Finally, the fourth factor (eigen value 1.0, 8.6% of the variance) loaded negatively on number of adults in the household and positively on parental education (Parent factor).

3.3.3 Prenatal care and pregnancy complications—To assess prenatal care and pregnancy complications an additional step was conducted to aggregate data. Maternal pregnancy complications (i.e. feet swelling, high blood pressure, premature labor) were summed as a cumulative risk variable as were delivery and neonatal complications (i.e. meconium exposure, hyperbilirubinemia (coded yes/no), fetal distress during delivery). A principal components factor analysis was then conducted on nine variables, resulting in four

factors. The first factor had an eigen value of 2.4 and accounted for 26.6% of the variance. This factor was positively related to pregnancy vitamin usage and seeking prenatal care (Positive Prenatal Care-factor). The second factor (eigen value=1.3, 14.1% of the variance) was positively related to month of prenatal care and negatively related to vitamin usage in trimester one (Negative Prenatal Care-factor). The third factor (eigen value=1.1, 11.9% of the variance) was positively related to number of previous pregnancies and maternal age (Mother Age-factor). Finally, the fourth factor (eigen value=1.0, 11.5% of the variance) was positively related to maternal pregnancy and neonatal complications (Perinatal Complication-factor).

3.3.4 Infant health status—Seven infant health status variables were then factor analyzed resulting in two factors. The first factor had an eigen value of 2.3 and accounted for 33.5% of the variance. The factor was positively related to gestational age, birthweight, height, and head circumference (Infant Size-factor). The second factor had an eigen value of 1.4 and accounted for 20.3% of the variance and was positively associated with 1 and 5 minute Apgar scores (Apgar-factor).

3.3.5 Maternal psychopathology—Scores on the SCL90R were also factor analyzed, yielding one factor with an eigen value=7.2 that accounted for 72.4% of the variance.

3.3.6 Other substance use—Eleven alcohol consumption variables were also factor analyzed. The resulting model yielded two factors. The first had an eigen value of 4.8 and accounted for 43.6% of the variance. All eleven variables (i.e. number of days of binge drinking, maximum number of drinks per day, each of the trimester estimates of absolute ounces of alcohol per day) were positively related to this variable (Alcohol abuse-factor). The second factor was negatively related to all of the heavy alcohol consumption variables (number of days of binge drinking. Maximum number of drinks per day) but was positively related to the averaged absolute ounces of alcohol consumed for each of the trimesters (AA-factor). Caffeine consumption for coffee, tea, and soda were summed to yield a summary variable of the total number of caffeinated beverage consumed per day during pregnancy. Finally, marijuana use during pregnancy was coded yes or no.

A forward hierarchical regression analysis was then done using the derived wave latency factor as the dependent variable. An alpha level of.05 was used for initial inclusion in the model and. 10 for retention. The initial step inputted the child's adjusted age, head circumference, gender, height, and weight but none of these factors were significantly related to the wave latency factor. The next step involved entering the potential confounding variables. The above mentioned covariates had to be related to either the wave latency factor or a maternal smoking variable to be entered into the model. An alpha level of.15 was chosen for screening these variables. The following variables were related to one or more of the estimates of smoking by trimester variable: SES-factor, Family maturity-factor, Parent-factor, Positive prenatal care-factor, Negative prenatal care-factor, Infant size-factor, Maternal psychopathology-factor, Alcohol abuse-factor, Total daily caffeinated beverages, and Marijuana use in pregnancy. Only AA_factor, Perinatal complications, and the Momage factor were related to the wave latency factor scores. The resulting model included only the Perinatal complications factor and the AA_factor ($F(2,169) = 5.45$, $p < .005$, R-Square=.061). Maternal smoking group level was then entered into the model and accounted for additional unique variance (R-square change =. 052; $F(1,168) = 9.82$, $p < .002$).

To assess the relative gains in variance explained from quantifying maternal smoking exposure using a continuous variable rather than the ordinal variable of group status, the average cigarettes consumed for 3-months prior to pregnancy, each of the trimesters, and the overall average number of cigarettes consumed in the perinatal period was entered into the model instead of maternal smoking group level in the last step. Only average number of cigarettes

consumed in the perinatal period accounted for additional unique variance (R-square change=. 064; (F (1, 168) = 12.2, p <.001).

4. Discussion

Deficits in auditory processing may be one of the neurodevelopmental consequences of maternal smoking during pregnancy that leads to later language and reading deficits. Fast auditory brainstem responses were used to assess differences in the sensory processing of auditory stimuli among infants with varying degrees of prenatal cigarette exposure. Maternal smoking during pregnancy was associated with a decreased latency in auditory brainstem responses and the relationship was dose-responsive. These results suggest that infants of mothers who smoked in pregnancy have disruption in their sensory encoding of auditory information. These results also provide converging evidence with animal models showing that exposure to chronic nicotine activation in rat pups is linked to decreased latency in stimulus detection as well as to alterations in responsiveness of ACh pathways in the cerebral cortex and poorer performance on an auditory-cued active avoidance task [53].

Examination of the individual wave forms suggested the strongest relationship was on Wave 5 although similar effects were observed on Wave 1 and 3 latencies. If nicotine facilitates the propagation of the action potential along the auditory nerve, the stronger relationships observed on Wave 5 may be the result of the cumulative effect of the facilitation along the pathway. The relationship between the time elapsed between Wave 1 and Wave 5 (V-I latency), which is recognized as an index of speed of conduction of the signal [58], and maternal smoking also supports this idea. These findings suggests that both middle latency and central auditory responses should be sampled as well to determine if there is an increase in the magnitude of the effect as the signal is transmitted from the brainstem to the central auditory system.

Quantification of exposure in human studies is often complex. Although using maternal smoking level as a continuous measure accounted for slightly more variance than did the maternal smoking dosage group, the magnitude of the gain was trivial (1.4% of the variance). Although number of cigarettes per day would appear to be a more refined measure than the dosage group level used in the study, this may be misleading in that there is considerable variability in actual intake of tobacco smoke and its contaminants for individuals with comparable levels of smoking behavior as defined by the number of cigarettes per day. Individual differences in smoking topography, including depth of inhalation, puff frequency, and puff duration, result in dramatic differences in exposure levels [74,75]. Maternal blood cotinine levels obtained at birth should theoretically provide a better estimate of exposure but the validity of this measure is limited by variability in duration of delivery and timing of the collection relative to the delivery and the last available opportunity for the mother to smoke. With a half-life of 18 hours, cotinine levels in women who self-reported smoking at high levels may have been low if an extended delivery and hospitalization prevented them from engaging in their typical smoking habit. The evidence for a dose-response relationship between maternal smoking and decreased ABER latencies in this study is provided by the convergence of the results into a similar pattern of relationships despite the limitations of each index of exposure.

Postnatal exposure to tobacco smoke was not found to be a significant factor in producing the ABER results. There were no significant relationships between latencies of the waves and postnatal urinary cotinine values of the infant obtained at the 6-month visit. A significant negative linear relationship between mother's urinary cotinine value at 6-months and Wave 5 latency was found but this relationship was no longer significant after accounting for the average number of cigarettes used during pregnancy. This pattern suggests that mothers' postnatal cigarette consumption was not adding unique variance to the prediction of Wave 5

latency but the same relationship exists when the variables are entered in reverse order, suggesting that prenatal and postnatal cigarette use are confounded in this sample.

Although women who smoked in pregnancy differed in terms of various social and physical environment variables collected that may threaten the internal validity of the study, the ABER responses were not related to most of these variables. The role of maternal smoking as compared to the potential confounders associated with maternal smoking in producing the obtained results was explored using a forward hierarchical model. There were numerous ways that mothers who smoked differed from mothers who did not smoke and some of these relationships were linearly related to dosage level. However, the only factors that also influenced the latencies of the ABER was perinatal complications and maternal drinking behavior and the obtained effects were in the opposite direction of the maternal smoking effect.

The impact of perinatal complications and maternal drinking on ABER latencies appears to be consistent with other neurotoxic exposures and medical conditions (i.e., lead exposure [62]; maternal cytomegalovirus infection [76], and Down's Syndrome [77]). These fetal insults may have in common a disruption to the myelin of the auditory nerve, which would result in delayed transmission of the auditory signal. Prenatal alcohol exposure has been repeatedly found to disrupt myelinization [78,79] and evidence has been obtained that ABER latencies are prolonged in rat pups across the lifespan after a history of alcohol exposure [80,81]. It is unclear to what extent other exposures that may co-occur with maternal cigarette usage, such as lead and maternal cytomegalovirus, may also be impacting ABER responses in this sample as they were not assessed.

The characteristics of those seen at 6-months compared to those not seen suggest that issues related to substance use may have contributed to reluctance to participate in the study for some participants. Although those not seen at 6-months reported higher levels of cigarette use prior to knowing that they were pregnant, this group did not differ in the report of their use of cigarettes during pregnancy. The lack of continued group differences in reported use of cigarettes is surprising as this group had maternal blood cotinine levels that were significantly higher than those who were seen and the average magnitude for the not-seen group was comparable to the levels found in the moderate to high dosage level groups. These results suggest that those who refused to continue to participate in the study may have been less accurate in reporting their cigarette usage during pregnancy.

Our attrition rate for ABERs not obtained among those seen at 6-months was 26.8%, which is fairly comparable to that of other infant testing procedures used in other experimental laboratories (28.6% [82] and 22.0% [83]) and more specifically, in administering ABERS in a similar context (25.5% [61]). When infant and family characteristics of those who successfully produced an ABER at the 6-month visit were contrasted to those who did not produce an ABER, differences in maternal birth cotinine levels were found. Higher cotinine levels were found in those who did not give an ABER sample when compared to those that did. This suggests that the obtained results may underestimate the impact of maternal smoking as some of the infants who were heavily exposed (mean birth cotinine value 35.18) were not able to be appropriately sampled.

To appropriately collect the ABER sample, infants needed to fall asleep during their 2 to 3 hour visit at the laboratory and allow us to attach the sensors and the tubephone in their ear. Although the majority of infants were able to do this with no problem, there was a subset of infants who were unable to fall asleep or who would awaken when the examiner attempted to attach the sensors or place the tubephone in the infant's ear. It is possible that those who were more heavily exposed may have greater disruption to their sleep patterns and general arousal regulation as these effects have been found repeatedly in tobacco-exposed individuals [84–

87] and that these characteristics may have interfered with our ability to obtain a sample from them. To further examine the relationship between maternal smoking and ABER responses, it may be more preferable to sample newborns or infants under 3-months of age to increase the infant's sleep need and reduce the attrition rates found in our study.

Low level auditory processing problems have been hypothesized as one of the mechanisms by which subtle speech perception problems evolve into deficits in phonological skills and reading development [88]. The auditory brainstem response indexes the initial neurophysiological encoding of auditory stimuli and disruption to this encoding may impact the perception of the phonemic characteristics of speech sounds. Children with deficits in phonemic perception and language development have demonstrated a similar alteration of fast auditory brainstem responses [64,65], suggesting the effect found in our sample may have an impact on their later speech and language development. Alterations in auditory processing in infancy have been found to be predictive of later language [89] and reading difficulties [90], suggesting that following the developmental trajectory of the altered ABER responses may be valuable in aiding our understanding later language and reading deficits observed in children with a history of prenatal tobacco smoke exposure.

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Table 1

Characteristics of Parents in Different Smoking Groups (N=172)

	Smoking Group				
Characteristic	**Control n=57**	**Light (<10/day) n=42**	**Moderate (10 to 19/day) n=58**	**Heavy (20+/day) n=15**	**Statistic**
Mothers Age/yrs	26.73 (4.85)	24.85 (5.45)	24.93 (5.33)	27.07 (6.75)	F(3,166)=1.768, ns
Fathers Age/yrs	28.27 (5.49)	27.79 (6.6)	28.04 (6.6)	31.0 (8.49)	F(3,129) =.79, ns
Marital Status (% Married or with partner)	75.00%	47.50%	42.10%	33.30%	$X^2(6)=33.07$, p<.001***
Mothers Education (% some college or greater)	75.00%	44.70%	47.20%	33.30%	$X^2(9)=39.04$, p<.001***
Fathers Education (% some college or greater)	79.10%	44.40%	34.00%	53.80%	$X^2(9) = 27.67$, p <.01***
Income Category (% < $35,000/yr)	21.10%	55.00%	42.10%	73.30%	$X^2(12) = 7.46$, p <.01***
Race (% Caucasian)	64.30%	62.50%	77.60%	80%	$X^2(12) =14.76$,ns
Insurance Type (% Medicaid)	35.80%	72.50%	66.70%	66.70%	$X^2(3) = 16.37$, p <.01***
Parity	1.15 (1.43)	1.51 (1.78)	2.07 (1.99)	2.64 (1.45)	F(3,158) =4.19, p <.01***

* Delineates a significant linear trend <.05,

** Delineates a significant linear trend <.01,

*** Delineates a significant linear trend <.001

Table 2

Characteristics of Infants in Different Smoking Groups (N=172)

	Smoking Group				
Characteristic	**Control n=57**	**Light (<10/day) n=42**	**Moderate (10 to 19/ day) n=58**	**Heavy (20+/day) n=15**	**Statistic**
Adjusted Age (Days)	194.4 (18.9)	194.5 (21.3)	199.3 (23.4)	192.9 (21.4)	F(3,168)=.75, ns
Sex (% Male)	42.90%	58.50%	50%	46.70%	X^2 (3) = 2.38, ns
Gestational Age	38.92 (1.27)	38.78 (1.33)	38.28 (1.41)	38.93 (1.09)	F(3,165) = 2.65, p =.05
Birthweight (gms)	3419.98 (469.87)	3317.61 (520.29)	3172.43 (414.25)	3131.33 (286.33)	F(3,166)=3.51, p <.05**
Birth Length/cm	51.68 (2.39)	50.78 (3.05)	50.3 (2.39)	50.66 (1.72)	F(3,166)=2.98, p <.05**
Head Circumference (cm)	33.99 (1.6)	33.73 (1.66)	33.52 (1.9)	33.7 (1.75)	F(3.164)=0.69, ns
Apgar 1	8.0 (0.8)	7.9 (1.18)	8.22 (.75)	7.8 (0.86)	F(3.166)=1.52, ns
Apgar 5	8.98 (.23)	8.88 (.4)	9.03 (.18)	9.0 (0)	F(3,166) = 2.95, p <.05
Preterm %	0.0	4.9%	5.2%	0.0	X^2 (3) = 3.70, ns
6 Month MDI	93.25 (6.47)	93.83 (7.02)	92.05 (8.62)	90.13 (8.26)	F(3,167)=1.14, ns
6 Month PDI	91.13 (12.19)	93.14 (11.94)	90.02 (13.11)	93.27 (17.09)	F(3,167)=.59, ns

* Delineates significant linear trend <.05,

** Delineates significant linear trend <.01,

*** Delineates significant linear trend <.001

Table 3

Number of Cigarettes per Day and Birth Cotinine Levels by Different Smoking Groups (N=172)

	Smoking Group				
	Control	**Light (<10/day)**	**Moderate (10 to 19/ day)**	**Heavy (20+/day)**	
	n=57	**n=42**	**n=58**	**n=15**	**Statistic**
3 mo Prior	0	10.5 (6.2)	21.0 (5.1)	25.3 (9.3)	F(1,168)=596.6, p <.000
1st Trimester	0	6.9 (4.4)	16.0 (6.1)	23.7 (8.6)	F(1,168)=462.0, p <.000
2nd Trimester	0	1.8 (2.9)	7.6 (5.7)	23.0 (11.3)	F(1,168)=236.8, p <.000
3rd Trimester	0	1.1 (1.8)	7.2 (5.4)	17.9 (9.7)	F(1,168)=218.4, p <.000
Birth Blood Cotinine[1]	.62 (4.0)	3.4 (10.1)	16.6 (29.6)	41.8 (89.9)	F(1,105)=13.95, p <.000

[1] Data available on 42 controls, 23 light, 36 moderate, and 8 heavy smokers.

Table 4

Correlation Matrix Between Self-Report of Cigarette Use and Cotinine Levels(n=172)

	3 Months Prior Cig/Day	1st Trimester Cig/Day	2nd Trimester Cig/Day	3rd Trimester Cig/Day	Log of Cotinine Maternal Blood at Birth	Log of Cotinine Maternal Urine at 6-months	Log of Cotinine Infant Urine at 6-months
Overall Average Cig/Day	.876***	.899***	.834***	.784***	.411***	.597***	.340***
3 Months Prior Cig/Day	-	.824***	.555***	.530***	.271**	.577***	.273**
1st Trimester Cig/Day		-	.650***	.542***	.279**	.589***	.336***
2nd Trimester Cig/Day			-	.800***	.466***	.397**	.250**
3rd Trimester Cig/Day				-	.507***	.435***	.199*
Log of Cotinine Maternal Blood at Birth					-	.208*	ns
Log of Cotinine Maternal Urine at 6-months						-	.368***

T p <.10,

* p <.05,

** <.01,

*** <.001

Table 5

ABER Wave Latency[1] in Different Smoking Groups (N=172)

	Smoking Group				
	Control	**Light (<10/day)**	**Moderate (10 to 19/ day)**	**Heavy (20+/day)**	
	n=57	**n=42**	**n=58**	**n=15**	**Linear Trend Statistic**
Wave 1	1.520 (.024)	1.502 (.028)	1.485 (.024)	1.450 (.044)	t (1, 154)= −1.53, p <.128
Wave 3	3.250 (.038)	3.180 (.045)	3.176 (.038)	3.136 (.071)	t (1,165)= −1.69, p <.093
Wave 5	5.865 (.054)	5.695 (.063)	5.693 (.053)	5.529 (.099)	t (1,169)= −3.25, p <.001
V-I Latency	4.382 (.603)	4.192 (.361)	4.211 (.220)	4.076 (.220)	(t (1,154)= −2.76, p <.007

[1]Latency values for the waves represented means by group after adjusting for the child's age in days at the time of the assessment and are in msec.

Table 6

Correlation Matrix Between Cigarette Use and ABER Latencies[1](n=172)

	Overall Average Cig/Day	3 Months Prior Cig/ Day	1st Trimester Cig/Day	2nd Trimester Cig/Day	3rd Trimester Cig/Day	Log of Cotinine Maternal Blood
Wave 1	−.138^{T}	−.073	−.114	−.141^{T}	−.192*	−.257**
Wave 3	−.163*	−.162*	−.137^{T}	−.133^{T}	−.109	−.075
Wave 5	−.233**	−.195**	−.219**	−.194**	−.183*	−.052
V-I Latency	−.197*	−.206**	−.201**	−.131^{T}	−.098	.012

^{T}p <.10,

*p <.05,

**<.01,

***<.001

[1]After adjusting for child's age