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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.

1. Introduction

Although smoking in pregnancy is discouraged by the medical community and the overall acceptance of smoking has declined in American culture [3,74], 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 [11–15]. Although it is fairly common for women to reduce their tobacco use during pregnancy, the majority continue to smoke throughout the pregnancy [7,12,31]. In 2002, 11.4% of all mothers reported smoking during pregnancy on birth certificates [13] but this is most likely an underestimate of actual use.

Aspects of the teratogenic impact of maternal smoking during pregnancy have been investigated for over 50 years with reduction in birth weight [82,88] being a consistent finding since the original observation in 1957 [81]. Other negative perinatal outcomes, including increased risks of spontaneous abortion [85], prematurity [19], oral clefting [86], neonatal death [85], and Sudden Infant Death Syndrome [65,80], 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 [8,9,20–84].

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 [23] and impairments in neonatal auditory habituation on the Brazelton Neonatal Behavioral Assessment Scale [7] has been reported repeatedly (e.g., [49–69]). Using polygraphic studies of sleep, Franco et al. [34] 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 [51]. In the Ottawa Prenatal Prospective Study (OPPS), at 12 and 24 months, tobacco-related differences were found [35] on an auditory cluster derived from the Infant Behavior Record of the Bayley Scales of Infant Development (BSID [1]). When these children were four to seven years of age, deficits in performance on auditory, but not visual, vigilance tasks were found [52] and, among 6- to 11-year-olds, poorer performance on a central auditory processing task was found [61], 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 [34,36–40] found later in adulthood [41]. In different samples that provide converging evidence regarding an underlying auditory deficit in children of smokers, prelinguistic skills in 6-month-olds [51] and vocalization of

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vowel–consonant combinations in 8-month-olds [67] were delayed in children of women who smoked in pregnancy. Among a sample of preschoolers, vocabulary expression [53] 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; [64]), 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 [43–62]. A similar facilitation of response has been found in adult human smokers using fast and middle latency auditory evoked responses [25–46]. 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 [57]. 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 [76]. 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 ms after stimulation are known as fast auditory responses or the Jewett Sequence [59,79] and are used to assess peripheral sensory encoding. Such responses are known to be altered by various teratogens [61,62] and certain genetic abnormalities [30]. In addition, reduced latencies have been found in children with phonemic language and reading deficits [70,71], 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 1/2 pack of cigarettes a day (<10 cigarettes), between 1/2 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 h 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 [89]. 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) were then calculated using the quantity-frequency-variability interview technique [10]. 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, [20]). Medical information and information about tobacco and other drug use were 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 h), and a urine sample to assess for exposure to illicit drugs. Women were excluded from participation