Neurotoxicology and Teratology 44 (2014) 81–88

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Prenatal tobacco exposure and response inhibition in school-aged children: An event-related potential study

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ARTICLE INFO

Article history:
Received 14 March 2014
Received in revised form 4 June 2014
Accepted 5 June 2014
Available online 16 June 2014

Keywords:
Cigarette
Event-related potentials
Go/No-go
Inhibition
Nicotine
Pregnancy

ABSTRACT

Prenatal cigarette smoke exposure (PCSE) has been linked to problems in behavioral inhibition and attention deficit hyperactivity disorder in children in several epidemiological studies. We used event-related potentials (ERPs) to examine the effects of PCSE on neural correlates of inhibitory control of behavior. In a prospective longitudinal study on child development in the Canadian Arctic, we assessed 186 Inuit children (mean age = 11.3 years) on a visual Go/No-go response inhibition paradigm. PCSE was assessed through maternal recall. Potential confounders were documented from a maternal interview, and exposure to neurotoxic environmental contaminants was assessed from umbilical cord and child blood samples. PCSE was not related to behavioral performance on this simple response inhibition task. Nevertheless, this exposure was associated with smaller amplitudes of the N2 and P3 components elicited by No-go stimuli, suggesting an impairment in the neural processes underlying response inhibition. Amplitude of the No-go P3 component was also inversely associated with behavioral measures of externalizing problems and hyperactivity/impulsivity in the classroom. This study is the first to report neurophysiological evidence of impaired response inhibition in school-aged children exposed to tobacco smoke *in utero*. Effects were found on ERP components associated with conflict processing and inhibition of a prepotent response, indicating neurophysiological deficits that may play a critical role in the attention and behavior problems observed in children with PCSE.

1. Introduction

Maternal cigarette smoking during pregnancy has been associated with behavior problems among the exposed offspring in several epidemiological studies (Batstra et al., 2003; Braun et al., 2008; Brook et al., 2006; Kotimaa et al., 2003; Obel et al., 2009; Robinson et al., 2010; Rückinger et al., 2010; Wakschloag et al., 2010). These children are at increased risk for externalizing behavioral problems, conduct disorder, and attention deficit hyperactivity disorder (ADHD), all of which are characterized by impulsive behavior. Cognitive assessments in these children have revealed impairments in executive function, notably in inhibitory control (Cornelius et al., 2011; Huijbregts et al., 2008; Julvez et al., 2007). The mechanisms of action for these adverse neurobehavioral effects have not been determined, but they have been hypothesized to reflect dysfunction in the monoamine and cholinergic neurotransmitter systems (Baler et al., 2008; Blood-Siegfried and Rende, 2010; Gold et al., 2009; Muneoka et al., 1997; Slikker et al., 2005; Xu et al., 2001).

Most studies investigating the relation of prenatal cigarette smoke exposure (PCSE) to behavior problems and cognitive impairments have relied on standard behavioral and neuropsychological assessments. Neurophysiological measures, such as event-related potentials (ERPs), could provide additional information on how PCSE impairs the brain processes underlying executive control of behavior and help elucidate the mechanisms of action responsible for its adverse neurobehavioral effects. We recently reported an association of PCSE with increased externalizing behavior problems and ADHD-related behaviors, as measured by behavioral questionnaires completed by the classroom teacher, in school-aged Inuit children from the Canadian Arctic, where tobacco smoking is a major public health issue (Desrosiers et al., 2013). This population is also exposed to neurotoxic environmental contaminants from their traditional diet based on hunting and

Abbreviations: ADHD, attention deficit hyperactivity disorder; DBD, Disruptive Behavior Disorders Rating Scales; ECCDS, Environmental Contaminants and Child Development Study; ERN, error-related negativity; Hg, mercury; Pb, lead; PCB, polychlorinated biphenyls; Pe, error positivity; PCSE, prenatal cigarette smoke exposure; PFC, prefrontal cortex; TRF, Teacher Report Form.

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http://dx.doi.org/10.1016/j.ntt.2014.06.003
0892-0362/

fishing, including lead (Pb), methylmercury, and polychlorinated biphenyls (PCBs) (Muckle et al., 2001), which have been related to behavioral problems and cognitive impairments similar to those associated with PCSE (Boucher et al., 2012a,b). In the present study we used ERPs to examine the neurophysiological correlates of PCSE-related impairments in inhibitory control in our prospective birth-cohort of Inuit children, after statistical adjustment for other neurotoxic exposures.

2. Methods

2.1. Participants

The study participants were 204 school-aged Inuit children from Nunavik, a region of Québec located north of the 55th parallel, about 1500 km from Montreal. These children were originally recruited in the Cord Blood Monitoring Program (1993–1998), which was designed to document levels of environmental contaminants and nutrients in newborns in Arctic Québec (Dallaire et al., 2003). Six of these children also participated in the Environmental Contaminants and Child Development Study (ECCDS; 1996–2000) (Boucher et al., 2014; Jacobson et al., 2008), which was initiated during the latter part of the Cord Blood Monitoring Program, and one child was recruited only for the ECCDS.

Assessments were conducted between September 2005 and April 2007 in the three largest Nunavik villages when the children averaged 11.3 years of age. Participants who resided in other communities were transported by plane to one of the larger villages for testing. A maternal interview was conducted during the child assessment to document demographic background, smoking, alcohol and drug use during pregnancy as well as other maternal characteristics. Inclusion criteria were age between 9.0 and 13.0 years, birth weight $\geq$2.5 kg, gestation duration $\geq$35 weeks, no known neurological or clinically significant developmental disorder, and no medication for attention problems. Two participants with a history of epilepsy, two with a history of head trauma associated with loss of consciousness and/or requiring hospitalization, one with multiple sclerosis and one with a history of meningitis were excluded after data collection. Written informed consent was obtained from a parent of each participant; oral assent, from each child. The research was approved by the Laval University and Wayne State University ethics committees.

2.2. Go/No-go protocol

Each participant was seated 57 cm from a 43-cm flat panel monitor on which letters were displayed centrally within a 7 × 7 cm space. The child held a button box in his/her hand and was instructed to press the button as quickly and accurately as possible with his/her index finger to all individually presented letters (the "Go" trials) except the target "X" (the "No-go" trials). The stimuli were presented for 500 ms, with random inter-stimulus intervals ranging between 1200 and 1400 ms. The first block consisted of 40 Go trials and served to prime Go responses within the second. This second block consisted of 126 Go trials (70%) randomly intermixed with 54 No-go trials (30%). Correct and incorrect responses were tabulated. Mean reaction time (RT; time between stimulus onset and button press) and response accuracy (% Correct) for Go and No-go trials during the second block of trials were computed. Data from the initial block of 40 Go trials were not analyzed (Burden et al., 2011).

Response inhibition in the Go/No-go task employed in this study has been shown to be associated with increased activity in the prefrontal cortex (PFC; Casey et al., 1997). The stimulus-locked ERPs elicited during this task include two late-latency components associated with the task conditions, the N2 and the P3 (Boucher et al., 2012a; Davis et al., 2003). The N2, which is maximal >300 ms post-stimulus over frontal electrode locations, has been attributed by some investigators to detection of a conflict regarding whether to inhibit a response (Donkers and van Boxtel, 2004; Falkenstein, 2006); by others, to conflict between competing Go and No-go decisions without regard to inhibition (Randall and Smith, 2011). The P3, maximal ≈500 ms post-stimulus at centro-parietal electrodes, shows enhanced activity for No-go stimuli and is generally thought to reflect the amount of resources needed for task processing and/or efficiently inhibiting a motor response (Davis et al., 2003; Smith et al., 2007).

In addition, response-locked ERPs are obtained following erroneous motor responses (*i.e.*, false alarms), offering a window on brain processes underlying error monitoring. These ERPs show two successive components: (1) the "error-related negativity" (ERN), maximal over fronto-central electrodes ≈80 ms after an incorrect response, which is thought to reflect the dynamics of response selection and conflict; and (2) the error positivity (Pe), peaking 200–400 ms after an incorrect response over central electrodes, which is thought to reflect the conscious recognition, or motivational significance, of an error (Hughes and Yeung, 2011; Overbeek et al., 2005).

2.3. EEG recording and analyses

The electroencephalogram (EEG) was recorded with 30 Ag–AgCl electrodes placed according to the international 10–20 system (Jasper, 1958), referenced online to vertex (Cz) electrode, with forehead ground. The electro-oculogram (EOG) was recorded from bipolar miniature electrodes placed vertically above and below the right eye. Impedance was kept <10 kΩ. EOG and EEG gains were amplified with gains of 5000 and 50,000 respectively. The bandpass filter was 0.1–30 Hz, and a 60-Hz notch filter was engaged. The digitization rate was 200 Hz.

ERPs were derived and analyzed using Brain Vision Analyzer 2.0 (Brain Products, Munich, Germany) software. EEG channels were re-referenced offline to linked earlobes. EOG correction (Gratton et al., 1983), artifact rejection (±100 μV) and baseline correction (100 ms) were applied. All responses occurring 200–1600 ms post-stimulus onset were considered valid. ERPs were averaged for "Correct Go", "Correct No-go" and "Incorrect No-go" responses separately. The "stimulus-locked" segments, which are measured in relation to when the stimulus first appeared on the screen, were segmented 100 ms before and 1000 ms after stimulus onset; the "response-locked" segments, which are measured in relation to when the child pressed the button, were segmented 300 ms before and 500 ms after button press. Each ERP component was examined at the electrode site showing the maximum (P3, Pe) or minimum (N2, ERN) voltage.[1] Peak amplitude (μV) and latency to peak (ms) of the stimulus-locked N2 (Fz; 250–500 ms) component were identified using automatic detection. Mean amplitude values were computed for the stimulus-locked P3 component (Pz; 400–700). Mean amplitude values were also computed for both response-locked components: ERN (FCz; 0–125 ms) and Pe (Cz; 100–500 ms).

Twelve participants were excluded after data analysis for the following reasons: technical problems during recording ($n = 4$); too much noise in the EEG signal to produce a reliable ERP waveform ($n = 3$); random responding on the task ($n = 2$); and insufficient number (<12 trials) of acceptable trials in their stimulus-locked ERP average ($n = 3$). These excluded participants did not differ from the remaining children in terms of PCSE ($\chi^2_{(1)} = 0.766$, $p = 0.381$). An additional 28 children were excluded from the analyses of the response-locked components because of an insufficient number of incorrect No-go trials in their averaged ERP waveform (<8 trials). Among the remaining participants, the mean number of epochs

[1] Examination of the topographic distribution of the Go/No-go response across the six midline electrode sites (Fz, FCz, Cz, Pz, POz, and Oz) among the unexposed children showed that the interaction effect between the Go and No-go conditions on ERP amplitude was maximal at Fz for N2, and at Pz for P3.