



Deficits in arithmetic error detection in infants with prenatal alcohol exposure: An ERP study

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ABSTRACT

Prenatal alcohol exposure (PAE) is associated with a range of physical, cognitive, and behavioral problems, particularly in arithmetic. We report ERP data collected from 32 infants (mean age = 6.8 mo; SD = 0.6; range = 6.1–8.1; 16 typically developing [TD]; 16 prenatally alcohol-exposed) during a task designed to assess error detection. Evidence of error monitoring at this early age suggests that precursors of the onset of executive control can already be detected in infancy. As predicted, the ERPs of the TD infants, time-locked to the presentation of the solution to simple arithmetic equations, showed greater negative activity for the incorrect solution condition at middle-frontal scalp areas. Spectral analysis indicated specificity to the 6–7 Hz frequency range. By contrast, the alcohol-exposed infants did not show the increased middle-frontal negativity seen in the TD group nor the increased power in the 6–7 Hz frequency, suggesting a marked developmental delay in error detection and/or early impairment in information processing of small quantities. Overall, our research demonstrates that (a) the brain network involved in error detection can be identified and highly specified in TD young infants, and (b) this effect is replicable and can be utilized for studying developmental psychopathology at very early ages.

1. Introduction

Because most standard neuropsychological tests are complex and multifaceted, they provide little information about the specific aspects of CNS function that may be adversely affected. Phenotypically similar behavioral deficits seen in different disorders, such as fetal alcohol spectrum disorders (FASD) and attention deficit/hyperactivity disorder (ADHD), are difficult to distinguish despite different etiologies. Castellanos and Tannock (Castellanos and Tannock, 2002) have advocated going beyond descriptive symptom-based approaches to identify specific markers derived from cognitive neuroscience that are closer to the site of the primary causative agent than to the manifest behavioral phenotype. Identification of such markers can enable diagnosis of developmental disorders to go beyond behavioral deficits to investigate impairment linked to a specific brain region, circuit, chemical imbalance, or, in this

case, a pattern of neural activation. This information is particularly important when behavioral measures are not sufficiently sensitive in discriminating between infants who may perform poorly due to environmental differences unrelated to the pathology. The brain measure, by contrast, can be particularly useful for diagnosis when different patterns of neural activation consistent with deficits associated with the disorder can be identified and used to detect pathology.

In neurocognitive tasks examining event-related potentials (ERPs), commission of an error evokes a frontomedial negative deflection known as error-related negativity (ERN), which is generated by a burst of synchronized theta activity proceeding from the anterior cingulate gyrus (ACC; Gehring et al., 1993; Hoffmann and Falkenstein, 2011; Luu et al., 2004). This neural activation appears to reflect a general monitoring process that compares expected vs. perceived stimuli or correct vs. incorrect responses and is evoked in response to a violation of

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expectations. Perceiving erroneous information that violates our expectations appears to involve the same mechanisms elicited when actually committing an error (Tzur et al., 2010; Tzur and Berger, 2009, 2007). It is unlikely that the ACC specializes in numerical or other specific domains; instead, information on which specific expectations are based is believed to flow to the ACC from domain-specific brain areas: in the case of linguistic information, from areas dedicated to language, such as the left planum temporale and insula; in the case of numerical information, most likely the intraparietal sulcus (IPS). The ACC is believed to mediate the process of making comparisons and signaling when a violation/conflict is detected.

We have shown that when infants are presented with incorrect solutions to simple arithmetic equations, they show the expected middle-frontal negativity related to the detection of an error (Berger et al., 2006), suggesting that the basic brain infrastructure for the detection of errors and violations of expectations is already operational in the first year of life. Our ERP task, adapted from the Wynn numerosity paradigm (Wynn, 1992), does not require any response from or instruction to the subject. Wynn originally showed that infants as young as 5 months of age can discriminate between correct displays (e.g., $1 + 1 = 2$) and errors (e.g., $1 + 1 = 1$) in simple arithmetic problems involving small numbers of items. In her well-known paradigm using puppets, when the number of puppets displayed does not agree with the number previously seen being placed on a stage, typically developing infants look longer at the display than when the number agrees with their expectations (Wynn, 1996, 1995; Wynn and Chiang, 1998). We adapted this paradigm to the ERP methodology and presented it to the infants who viewed a videotape of puppets (Figs. 1b and 1c), which represented the same simple arithmetical equations (e.g., $1 + 1 = 2$ and $2 - 1 = 1$) used by Wynn. In our original study (Berger et al., 2006), we replicated Wynn's behavioral findings and extended them by showing that, in

response to equations with incorrect solutions, typically developing (TD) 7-month-old infants show greater negative activity in an ERP window that corresponds to the classic ERN. We showed in TD infants that such brain activity is reflected in the differential looking time of the infants to the incorrect vs. the correct conditions. However, to date, this finding has not been examined in atypically developing young infants (such as those with FASD, who are particularly at risk for impairment in number processing) to assess whether erroneous information is similarly

processed. In addition, the exact frequency band for this activation has not been specified. Although violation of expectations at the behavioral level using looking or fixation time have been extensively studied in infants (e.g., see Stahl and Feigenson, 2015), only a few studies have looked at the electrophysiological brain activity level. Reid and colleagues (Michel et al., 2017; Reid et al., 2009) studied violation of a goal within action sequences and found effects on the N400, a similar ERP component related to semantic violations, and the theta band frequency in infants at age 9 months but not younger. The only other EEG/ERP study specifically focusing on an ERN effect was conducted by Conejero et al. (2018), who displayed erroneous information to somewhat older participants (16- to 18-month-old toddlers) than those studied in Berger et al. (Berger et al., 2006), using a task based on puzzles that assemble animal figures, which can contain errors, such as an elephant's head on a chick's body. In that study, perception of the erroneous figures generated a power burst in the 6–7 Hz frequency band. This finding has also not been examined in atypically developing infants.

In the present study, we examined the specific brain activity signature of error detection to erroneous arithmetical equations in TD infants and in an atypically developing group comprised of infants born to women who heavily drank alcohol during pregnancy (Jacobson et al., 2017). FASD is the umbrella term for a range of disorders related to PAE, which differ in severity of symptoms. The most severe consequence of maternal drinking during pregnancy is fetal alcohol syndrome (FAS), which is characterized by a distinctive set of facial anomalies, including short palpebral fissures, thin upper lip, and flat philtrum; pre- and/or postnatal growth retardation; and microcephaly (Hoyme et al., 2005). These children also exhibit significant cognitive and/or behavioral problems. Children are diagnosed with partial FAS (PFAS) if they have 2 of the 3 key facial anomalies and growth retardation, microcephaly, or CNS deficits, as well as confirmed PAE. Arithmetic has been identified as a particularly sensitive developmental endpoint in FASD. Several prospective longitudinal studies have consistently indicated that arithmetic is the domain most strongly related to PAE (Coles et al., 1991; Howell et al., 2006; Jacobson et al., 2004; Streissguth, 1994). Although PAE is related to poorer performance on standardized tests of reading, spelling, and arithmetic, only the effect on arithmetic is dose-dependent and remains significant after statistical adjustment for IQ (Goldschmidt et al., 1996; Jacobson et al., 2011a).

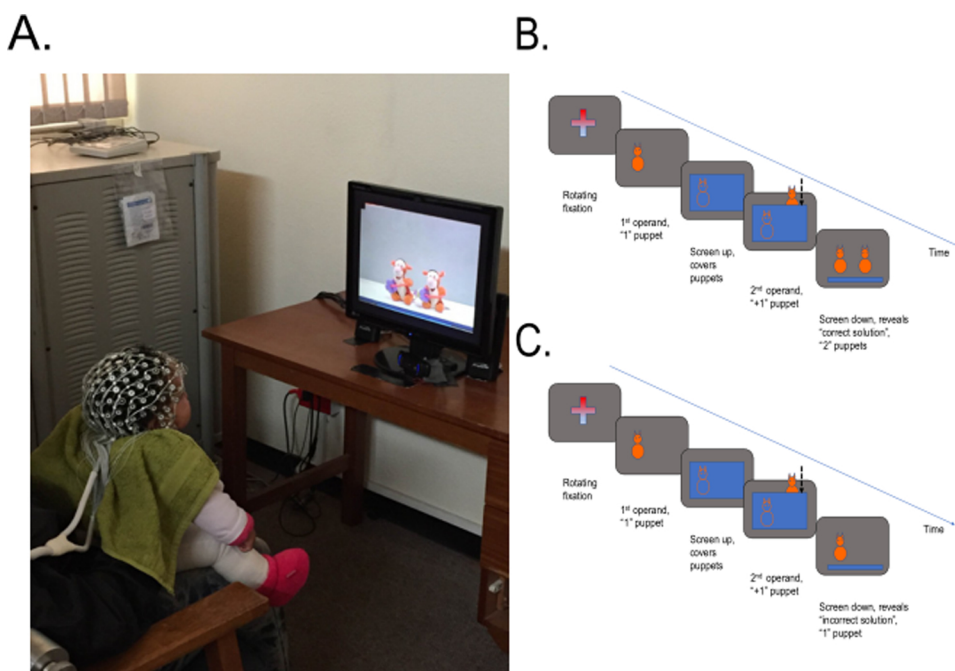


Fig. 1. Experimental Setup and Design. (A) One of the participants in the study wearing the geodesic net and watching the stimuli. These stimuli were the same as those used by Berger et al. (Berger et al., 2006): a puppet videotaped version of the different mathematical equations ($1 + 1 = 1$, $1 + 1 = 2$, $2 - 1 = 1$, and $2 - 1 = 2$), which were edited with an exact timing of the series of events within each type of trial; for example, (B) schematically represents the events for the correct equation $1 + 1 = 2$, which were "1 puppet displayed, a screen is raised up, a hand enters the scene with another puppet, the screen comes down, the correct solution of 2 puppets is revealed"; (C) schematically represents the events for the incorrect equation $1 + 1 = 1$, "1 puppet displayed, a screen is raised up, a hand enters the scene with another puppet, the screen comes down, the incorrect solution of 1 puppet is revealed".

In a pilot study using a subsample from our original Cape Town Longitudinal Cohort study (Jacobson et al., 2008), we administered the behavioral Wynn numerosity paradigm at 6.5 and 12 months and found that looking time on the numerosity test later predicted performance in numerical processing at 5 years of age (Jacobson et al., 2011b). These longitudinal data were collected in Cape Town, South Africa, where the prevalence of FAS in the Cape Coloured (mixed ancestry) population is estimated to be at least 18–141 times greater than in the U.S. (May et al., 2007) and is the highest reported rate of FASD in the world (May et al., 2016a). The population, comprised mainly of descendants of white European settlers, Malaysian slaves, Khoi-San aboriginals, and black Africans, historically provided the large majority of workers in the wine-producing region of the Western Cape Province. The high prevalence of FAS in this community is a consequence of very heavy maternal drinking during pregnancy (Croxford and Viljoen, 1999), due to poor psychosocial circumstances and the traditional *dop* system, in which farm laborers were paid, in part, with wine. Regular and heavy alcohol consumption persists in a high proportion (~30%) of women during pregnancy in this community (May et al., 2013, 2016b), facilitating recruitment of heavily alcohol exposed and nonexposed TD infants from the same population.

We have since recruited a second cohort of infants born to women interviewed prospectively during pregnancy from the same Cape Coloured community (Jacobson et al., 2017). This sample consists of TD infants whose mothers abstained or drank alcohol no more than minimally during pregnancy and those from the same community who were heavily exposed to alcohol *in utero*. The aims of this study were (1) to confirm our previous finding of an increase in ERP middle-frontal negativity in response to error detection in TD young infants, (2) to specify the exact brain activity frequency from which this negative deflection is generated in this age range in TD infants, and (3) to examine the degree to which an increase in ERP middle-frontal negativity in response to error detection is altered in atypical development, in this case in infants with heavy PAE, who are at high risk for impairment in number processing.

2. Methods

2.1. Participants

The sample consisted of 62 Cape Coloured infants (M age = 6.8 mo, $SD = 0.6$, range = 6.1–8.1 mo; TD group: M age = 6.9 mo, $SD = 0.5$, range = 6.2–8.0 mo; Exposed group: M age = 6.8 mo, $SD = 0.6$, range = 6.1–8.1 mo) born to women recruited between 2011–2014 at their first visit ($M = 38.7$ gestation weeks, $SD = 2.32$) to one of two antenatal clinics serving this community (Jacobson et al., 2017). The sample was recruited from an economically disadvantaged, poorly educated Cape Coloured community in Cape Town, where rates of alcohol use during pregnancy and of FAS are considered the highest in the world (May et al., 2016a, 2016c). CM, a developmental pediatrician, interviewed each mother at her first antenatal visit using a “gold standard” 2-week timeline follow-back procedure (Jacobson et al., 2002) regarding her alcohol consumption both at time of recruitment and around conception. Volume was recorded for each type of beverage consumed each day and converted to ounces (oz) of absolute alcohol (AA; 1 oz AA \approx 2 standard drinks). Any mother who reported drinking at least 14 standard drinks/week (\approx 1 oz AA/day) or engaging in binge drinking (\geq 4 drinks/occasion) was invited to participate in the study. A community-matched sample of Cape Coloured women who abstained or drank only minimally ($<$ 0.1 oz AA/day) was recruited. Exclusionary criteria included maternal age $<$ 18 years of age, HIV infection, and those with diabetes, epilepsy, or cardiac problems requiring treatment. Infant exclusionary criteria included major chromosomal anomalies, neural tube defects, multiple births, and seizures.

Timeline follow-back interviews were re-administered by CM at 4 and 12 weeks after recruitment. Data from the three interviews were

averaged to provide the following continuous measures of alcohol exposure: oz AA/day, oz AA/drinking occasion, and frequency of alcohol use (days/week) at time of conception and during pregnancy. Mothers were also interviewed regarding their frequency (days/month) of smoking (cigarettes/day) and illicit drug use (marijuana [“dagga”], methamphetamine [“tik”], cocaine, heroin, and methaqualone [“mandrax”]); days/month) during pregnancy.

Inclusion in the ERP data analyses meant that the infants’ behavior and the EEG trials met specific criteria (see below). Infants had at least 4 trials in each experimental condition with mean number of valid trials per infant for the correct ($M = 6.4$, $SD = 1.5$, range = 4–9) and incorrect ($M = 6.6$, $SD = 1.9$, range = 4–12) solution conditions. Number of valid trials did not differ between experimental conditions ($F(1,30) = 0.22$, $p = 0.641$, $\eta^2 = .007$) or between groups ($F(1,30) = 0.16$, $p = 0.689$, partial $\eta^2 = .005$).

Among the 62 infants tested, the following were excluded: 6 too fussy, 2 technical problems, and 22 insufficient usable ERP data after exclusion of trials based on the behavioral criteria (see explanation below in the procedure section) and/or excessive infant movement leading to noisy EEG recording, leaving a final sample of 32 infants (16/group). Our attrition rate was 48%, which is similar and even slightly lower than the attrition rate in infant ERP studies reported in a meta-analysis of 149 studies (Stets et al., 2012). Table 1 presents the background characteristics for the TD and alcohol-exposed groups.

2.2. Stimuli

Following Berger et al. (Berger et al., 2006), we presented the arithmetical equations using a videotape of a puppet theater (see Fig. 1). Preceding each trial, a colorful display was presented to attract the infant’s attention until the experimenter was confident that the infant was looking at the monitor. Each trial began with one or two puppets displayed for 4 seconds. A screen then came up and a hand appeared either inserting or removing one puppet from behind the screen. After this operation was completed, the soundtrack was silenced, and the screen stayed up for 600 ms, during which the baseline in the ERP analysis was calculated; the screen was then lowered revealing the solution to the equation. The positions of the puppets on the stage (right vs. left) were counterbalanced, and the different trial conditions (correct vs. incorrect solutions) were presented in a pseudorandomized order. Looking time was not collected during the ERP task because collecting these behavioral data would have altered the fixed time the stimulus (i.e., the solution to the equation) was presented. It would have required leaving the stimulus on the screen until the infant looked away, thereby lengthening the time needed to administer the task. In pilot testing, subject loss was increased because many infants soon lost interest in the longer version of the task.

2.3. Procedure

Mothers and infants were transported to our research laboratory by a research nurse and driver for assessment on the ERP and other infant tasks. Protection of human subjects’ approval was approved by Institutional Review Boards at Wayne State University and University of Cape Town Faculty of Health Sciences. At 6.5 months, the infants were given the ERP task; the Fagan Test of Infant Intelligence (Fagan and Singer, 1983), a measure of visual recognition memory and information processing speed predictive of later intellectual development (Colombo et al., 1991; Fagan and McGrath, 1981); and the Teller et al. (1986) Visual Acuity Card task (Carter et al., 2005).

Prior to the ERP task, the infant’s head circumference was measured by the research assistant and an appropriately sized 128-HydroCel Geodesic Sensor Net was placed on his/her head. During presentation of the stimuli, the infant was seated on his/her mother’s lap, 100 cm from the video monitor. The direction of the infant’s gaze was

Table 1
Sample Characteristics (N = 32).

	Typically Developing n = 16	Alcohol- Exposed n = 16	t or χ^2
Maternal Characteristics			
Socioeconomic status ^a	22.4 (9.0)	17.2 (6.3)	1.91
Education (years)	10.3 (1.7)	9.1 (1.5)	2.14*
Age at time of delivery	25.9 (6.1)	29.2 (5.4)	1.59
Pregnancy drinking At time of conception			
oz absolute alcohol/day	0.0 (0.0)	1.3 (1.0)	5.15***
oz absolute alcohol/occasion	0.0 (0.0)	3.8 (2.8)	5.54***
frequency (days/week)	0.0	2.0 (1.2)	6.31**
Across pregnancy			
oz absolute alcohol/day	0.0003 (0.001)	0.8 (0.7)	4.77**
oz absolute alcohol/occasion	0.1 (0.3)	4.0 (2.1)	7.41**
frequency (days/week)	0.002 (0.01)	1.4 (1.1)	4.90**
Pregnancy smoking (cigarettes/ day) ^b	6.1 (3.2)	9.0 (5.9)	1.28
Infant Characteristics			
Sex (% male)	68.8	43.8	2.03
Gestational age at birth (weeks)	39.4 (2.1)	38.5 (2.7)	1.12
Birthweight (g)	3056.3 (478.7)	2775.3 (380.1)	1.84†
Length at birth (cm)	48.6 (3.0)	48.3 (3.2)	0.20
Head circumference at birth (cm)	33.5 (1.9)	32.5 (1.2)	1.83†
Visual acuity			
Cycles/degree	7.0 (1.5)	6.1 (1.6)	1.64
Fagan Test of Infant Intelligence % novelty preference			
6.8 mo ^c	62.1 (7.0)	61.5 (4.4)	0.28
12 mo ^d	62.1 (4.4)	60.9 (7.4)	0.54
average	61.9 (4.6)	60.9 (4.9)	0.60
mean look duration(s)			
6.8 mo ^c	1.9 (0.4)	1.7 (0.4)	1.28
12 mo ^d	2.0 (0.4)	2.2 (0.4)	1.70
average	1.9 (0.3)	2.0 (0.4)	.007
Age at ERP Testing (months)	6.9 (0.5)	6.8 (0.6)	0.15

Note. Values are mean (SD).

^aHollingshead, 2011.

^bSmokers only (n = 8 typically developing; n = 13 alcohol-exposed).

^cMissing for 1 typically developing and 2 alcohol-exposed.

^dMissing for 2 typically developing and 1 alcohol-exposed.

†p < .10 *p < .05 **p < .001.

continuously recorded by the experimenter during the session to ensure that data would be based only on trials in which the infant looked at the screen throughout the entire trial stimuli presentation (see below). The mother was instructed to avert her eyes from the monitor during the entire trial and refrain from interacting with the infant during the assessment. The experimenter continuously verified that the mothers did not look at the stimuli or interact with the infant, and compliance

was high. The session was discontinued if the infant became fussy or ceased paying attention to the stimuli presentations.

A trial was considered usable only if the infant looked at the screen during the entire presentation of the sequence (initial presentation of either 1 or 2 puppets, screen going up, hand either adding or removing a puppet, screen down revealing the final “solution” of the equation). Only segments that met this strict behavioral criterion were analyzed.

2.4. EEG recording and preprocessing

Electroencephalographs (EEGs) were recorded using an EGI Hydro-Cel Geodesic Sensor Net and system (Electrical Geodesics, 2003; see Fig. 1a.); 128 electrodes were distributed on the scalp according to an adapted 10–20 method and were sampled at a rate of 250 Hz (Tucker, 1993). The electrode impedance level was kept under 40 K Ω , an acceptable level for this system (Ferree et al., 2001). During EEG recording, all channels were referenced to the Cz channel.

Preprocessing was conducted using the EEGLAB toolbox (Delorme and Makeig, 2004) operating in the MATLAB (Mathworks, Natick, MA) environment. The continuous EEG data were filtered with a 40 Hz band-pass and then segmented into 1 long trial starting 200 ms before and ending 1000 ms after the stimulus presentation onset (stimulus-locked). Only segments of trials that met the behavioral criteria noted above and free from artifacts (e.g., bad channel, blinks, eye movement) were further analyzed. Bad channels were replaced with a spherical interpolation of the neighboring channel values; the average number of channels interpolated across subject was 2.36 per trial, and the maximal number of channel interpolated channels in a trial was 16 out of the 128 electrodes.

Segments were averaged and re-referenced to the average of the channels across the scalp, after which a baseline-correction was conducted for 200 ms before the presentation onset. Baseline-corrected ERP data were averaged across subjects, resulting in an averaged segment ERP for each condition (grand average).

2.5. ERP extraction

To analyze the ERN component, we selected a group of 13 mid-frontal electrodes around and including Fz of the 10–20 system, comparable to the classic location of the ERN in the literature (e.g., Conejero et al., 2016; see Fig. 2, Panel C) and visual inspection of grand averages. Mean amplitudes of the evoked signal per condition were extracted within the time-window of 150–550 ms after stimulus onset for each subject.

2.6. Time-frequency analysis

Single-trial data were decomposed into their time-frequency representation using custom scripts written in MATLAB¹. The power spectrum of the EEG was multiplied by the power spectrum of complex Morlet wavelets (Press, 2019): $e^{-i2\pi ft} e^{-t^2/(2\sigma^2)}$, where t is time, f is frequency, and σ defines the width of the Gaussian taper of each frequency band. Frequency increased from 1 to 40 Hz in 1 Hz steps, whereas σ was set according to $n/(2\pi f)$, where n increases from 3 to 40 in 0.9487 cycle steps. Following convolution, the inverse fast Fourier transform was taken to reshape data back into individual epochs. Baseline activity, defined as the average power at each frequency band between -200 to 0 ms prestimulus, was subtracted from each data point within the corresponding frequency band, to produce event-related power estimates. Power was then averaged across trials separately for

¹ The custom scripts are based on the lectures (<http://mikexcohen.com/lectures.html>) in the book “Analyzing neural time series” (Cohen, 2014) and are available in the public domain: http://mikexcohen.com/book/AnalyzingNeuralTimeSeriesData_MatlabCode.zip

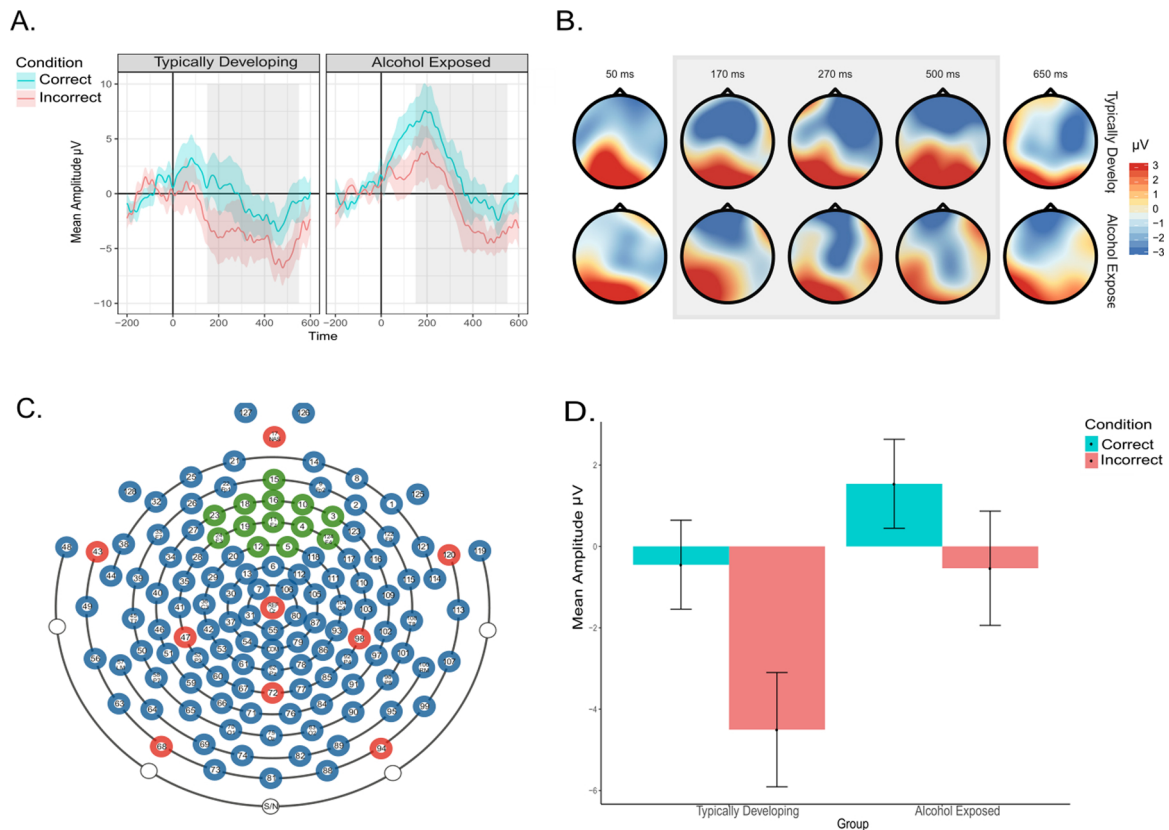


Fig. 2. ERP Results. (A) Grand-averaged ERP and (B) scalp voltage topomaps. Top row in both panels shows the results of the TD group and the bottom row shows the Alcohol-Exposed group. Note the gray rectangle marking the time-window between 150–550 ms. (C) Channel group (colored in green) over the mediofrontal area of the Geodesic 128 channels, localized approximately between and including Cz and Fz of the 10–20 system. (D) Mean amplitudes for each condition for each participant group (for interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

each electrode, for each condition, for each subject.

2.7. Potential confounding variables

Background variables were assessed for consideration as potential confounders of the effects of PAE on the two outcome measures: ERP amplitude and power in the 6–7 Hz frequency band (see Table 2 for list of confounders and their correlations with outcomes). Any control variable that was even weakly related ($p < 0.10$) to an outcome was considered a potential confounder of the effect of prenatal alcohol and adjusted statistically, after being centered, in all analyses of alcohol effects on that outcome.

3. Results

Although the whole sample was socioeconomically disadvantaged and poorly educated, TD mothers were slightly more educated than those in the alcohol-consuming group (Table 1). Most of the mothers of exposed infants concentrated their alcohol use to 1–2 days/week during pregnancy and drank, on average, 8 drinks/occasion, thus resulting in a binge pattern of consumption. All but 1 of the TD mothers abstained from drinking; the 1 TD mother consumed 2.5 drinks on one occasion during pregnancy. There were no significant between-group differences for cigarette smoking; none of the mothers reported using methamphetamine, heroin, cocaine, or methaqualone; and only 1 in each group used marijuana. There were no between-group differences regarding infant sex or age at ERP assessment. Although there was no difference between the two groups regarding gestational age at birth, alcohol-exposed infants tended to weigh somewhat less than those in the TD group. Of the 16 alcohol-exposed infants, 5 were diagnosed by expert

dysmorphologists with full FAS, the most severe form of FASD, and 1 with PFAS (see Jacobson et al., 2017). Although one infant in the alcohol-exposed group had a low acuity score, i.e., below the 5th percentile at 6.5 months (< 3.38 based on binocular acuity norms; Salomão and Ventura, 1995), no significant between-group differences were seen on the Teller acuity test (with or without inclusion of the single infant with the acuity deficit).

We conducted separate analyses for ERP amplitudes and frequency power (time-frequency analyses). The first step was to test whether we could replicate our previous findings in the TD infants (Berger et al., 2006). This is important, given the limited replicability of many findings in the field and the challenge in obtaining sufficient valid trials per condition with participants who are so young. We then examined the frequency power band(s) in which differences between the correct and incorrect conditions were seen. Next, we compared the ERP and frequency power responses to detect arithmetical errors in the TD infants with the alcohol-exposed group and tested whether continuous measures of maternal alcohol consumption during pregnancy correlated with the brain electrophysiological responses to error detection. Potential confounding variables that correlated (at $p < 0.10$) with the outcomes (socioeconomic status [SES] and mean novelty preference ages 6.5 and 12 months on the Fagan test in the ERP amplitude analyses; age of the child at testing in the time-frequency analyses) were entered as covariates.

3.1. ERP analysis

The data were analyzed using repeated measures analysis of covariance (ANCOVA), with correctness (correct vs. incorrect solution) as a within-subject variable and group (TD vs. alcohol-exposed) as a

Table 2
Relation of potential confounding variables to ERP (mean amplitude) and TF (mean power in 6–7 Hz frequency) outcomes; $N = 32$.

	Incorrect – Correct (Difference) ERP	Incorrect – Correct (Difference) TF
Maternal Characteristics		
Age at time of delivery	-.0846	.1036
Years of education	-.0306	-.1413
Socioeconomic status ^a	.3070 [†]	.0706
Pregnancy cigarettes/day ^b	.0515	-.1346
Infant Characteristics		
Birth weight (g)	-.2188	-.1231
Birth length (cm)	-.0457	-.2174
Head circumference at birth birth (cm)	-.1709	-.0563
Gestational age at birth (weeks)	.0043	.0680
Age at ERP testing (months)	-.1360	.4060*
Fagan Test of Infant Intelligence % novelty preference		
6.8 mo ^c	0.209	-.102
12 mo ^d	0.217	-0.001
Average	-0.293 [†]	-0.004
Mean look duration (s)		
6.8 mo ^c	-0.181	0.083
12 mo ^d	0.000	0.085
Average	-0.206	0.077
Age at ERP testing (months)	-.1360	.4060*

Values are Pearson r .

^a(Hollingshead, 2011).

^bSmokers only ($n = 8$ TD; $n = 13$ alcohol exposed).

^cMissing for 1 typically developing and 2 alcohol exposed.

^dMissing for 2 typically developing and 1 alcohol exposed.

[†] $p < 0.10$ * $p < .05$.

between-subject variable. SES and Fagan Test of Infant Intelligence % novelty preference were entered as covariates. As predicted, there was a main effect of correctness condition, with larger negative amplitudes for the incorrect condition compared with the correct one, $F(1,28) = 8.08$, $p < 0.01$, *partial* $\eta^2 = .224$ (Fig. 2). There was also a main effect for group, $F(1,28) = 4.49$, $p < 0.05$, *partial* $\eta^2 = .138$. Although the group \times correctness interaction was not significant, $F(1,28) = 0.83$, $p = 0.368$, the simple main effects were tested based on our *a priori* hypotheses and revealed that for the TD infants, the expected effect of correctness was significant, $F(1,28) = 5.60$, $p < 0.05$, *partial* $\eta^2 = 0.166$; in contrast, the alcohol-exposed infants did not show this pattern, $F(1,28) = 0.543$, $p = 0.467$, *partial* $\eta^2 = 0.019$. Moreover, the same pattern of results was found even after excluding the single infant that had relatively lower visual acuity from the alcohol-exposed group; the simple main effect for TD group remained significant: $F(1,27) = 5.570$, $p < 0.05$, *partial* $\eta^2 = 0.171$, whereas the simple main effect for the alcohol group remained insignificant, $F(1,27) = 0.804$, $p = 0.378$, *partial* $\eta^2 = .02$.

3.2. Time-frequency analysis

First, the data for the TD infants were analyzed using repeated measures analysis of variance (ANOVA) with frequency band (1–3 Hz, 4–5 Hz, 6–7 Hz, 8–12 Hz, 13–40 Hz) and correctness (correct vs. incorrect solution) as within-subject variables. There was a main effect for the frequency band, $F(4,60) = 11.56$, $p < 0.001$, *partial* $\eta^2 = .435$, and a significant frequency \times condition interaction, $F(4,60) = 3.42$, $p < 0.05$, *partial* $\eta^2 = .185$. Consistent with Conejero et al. (Conejero et al., 2018), planned comparisons showed that the difference between the correct and incorrect solutions was specific to (i.e., significant only for) the 6–7 Hz frequency band, $F(1,15) = 4.60$, $p < 0.05$ (Fig. 3). We then compared power for the 6–7 Hz frequency band in the TD and

alcohol-exposed infants, using repeated measures ANOVAs with trial type (correct vs. incorrect solution) as a within-subject variable and group as a between-subject variable. Age of the infant was entered as a covariate. There was a significant condition \times age interaction, $F(1,29) = 6.02$, $p < 0.05$, *partial* $\eta^2 = .172$, indicating that even within our restricted age range (6.2–8.8 months), there was a gradually increasing differentiation between the 6–7 Hz power in the incorrect vs. the correct conditions. We also found the expected group \times condition interaction, $F(1,29) = 4.43$, $p < 0.05$, *partial* $\eta^2 = .132$, showing a full crossover between the groups (Fig. 3); TD infants showed stronger power for the incorrect compared with the correct solution, simple main effect $F(1,29) = 4.231$, $p = 0.059$, *partial* $\eta^2 = .127$. In contrast, the alcohol-exposed infants did not show this pattern, $F(1,29) = 1.331$, $p = 0.268$, *partial* $\eta^2 = .0438$ (Fig. 3). Consistent with the findings in the ERP analysis, the pattern of results did not change with or without the single infant with lower visual acuity: the simple main effect was not significant for the alcohol-exposed group, $F(1,28) = 0.71$, $p = 0.413$, *partial* $\eta^2 = .02483$, whereas the effect remained significant for the TD group, $F(1,28) = 4.231$, $p = 0.059$, *partial* $\eta^2 = .131$.

3.3. Correlations between the electrophysiological brain measures and prenatal alcohol exposure

We conducted Pearson correlations to examine whether continuous measures of PAE were related to error detection. Higher amplitude of the theta 6–7 Hz frequency band power during error detection (incorrect minus correct) was associated with lower maternal oz AA consumed per drinking occasion, both at time of conception, $r = -0.32$, one-tail $p < 0.05$, and during pregnancy, $r = -0.41$, one-tail $p < 0.05$ (Fig. 3, Panel C). No significant associations were found between these brain activity measures and prenatal exposure to maternal smoking.

4. Discussion

The observed brain activity of the TD group suggests that these infants detected when there was an error in the arithmetic equation shown to them. These data confirm our previous findings that the increased middle-frontal negativity seen in error detection in children and adults is already evident in TD infants (Berger et al., 2006). The timing and topography on the scalp for this activity is consistent with our previous study. It can be considered an ERN-like effect (Tzur and Berger, 2009, 2007) and is compatible in topography and frequency, although earlier in its timing, with the N400 (Michel et al., 2017; Reid et al., 2009). The time-frequency analysis in the present study extends our previous findings by showing that, in infants, the difference between the correct and incorrect conditions is specifically within the power of the 6–7 Hz frequency, consistent with Conejero et al.'s (Conejero et al., 2018) report on toddlers. Our data thus provide further support for the claim that the basic brain circuitry involved in at least one important aspect of executive control, that is, the detection of errors, can be delineated with high specificity and is already functional before the end of the 1st year of life. These data are consistent with recent reports regarding other aspects of executive function (such as inhibitory control) in infants > 1 year of age (Holmboe et al., 2018). However, our data also indicate that the brain circuitry related to the detection of errors is not fully mature at this early age; the narrow 6–7 Hz time-frequency seen in infancy and toddlerhood later includes slower frequencies (i.e., 4–5 Hz), developing into the classic error-related negativity repeatedly found in older children and adults (Hoffmann and Falkenstein, 2011).

More importantly, in this study we further use our error-detection paradigm to examine this pattern of neural activation in a group of children with a serious developmental disorder at a very early age. By contrast to the TD infants, the alcohol-exposed group failed to show larger negative amplitudes in the incorrect condition, and the effect was even stronger in the time-frequency analysis. Moreover, the 6–7 Hz

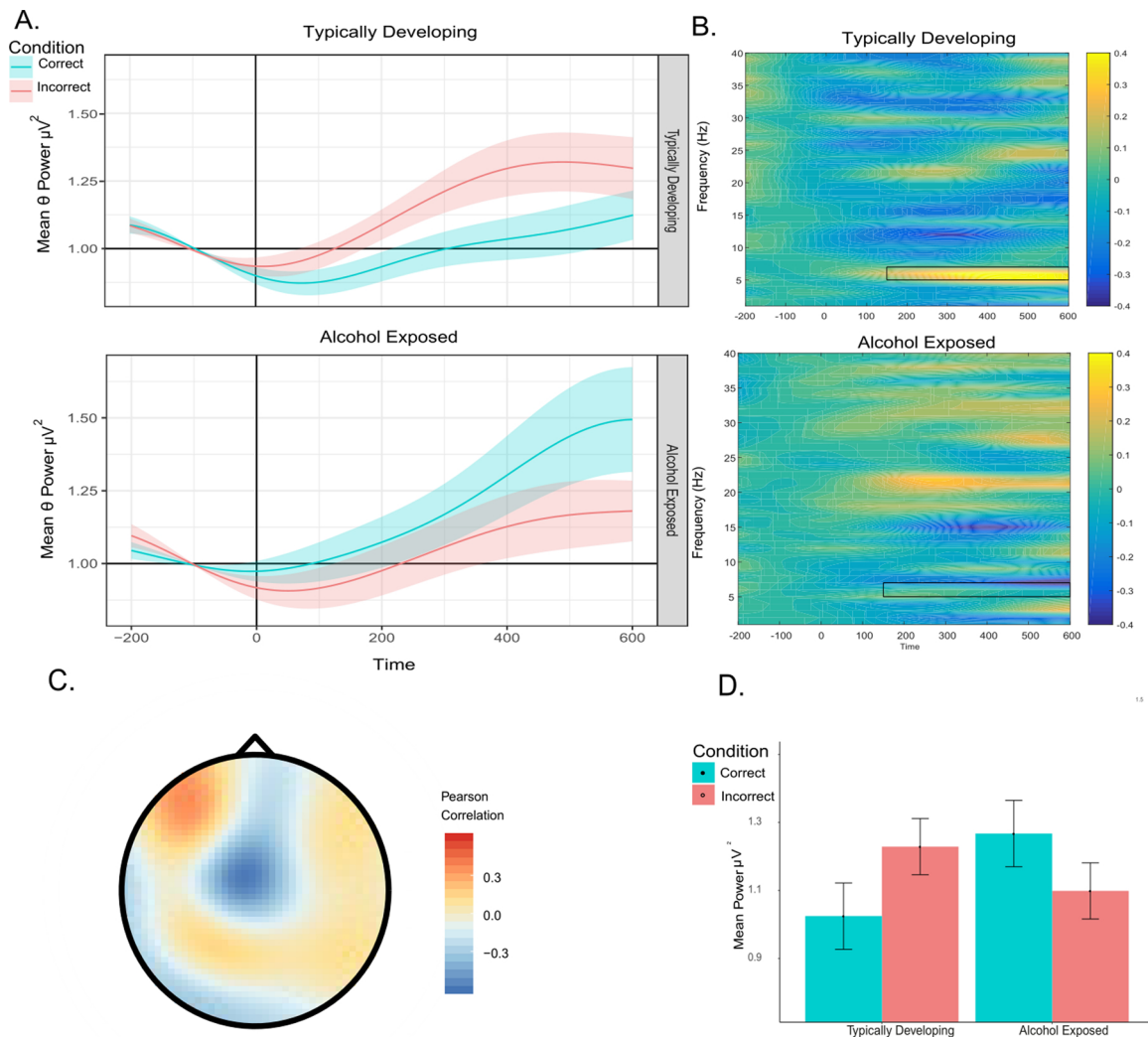


Fig. 3. Time-Frequency Results. (A) Grand-averaged power of the 6–7 Hz frequency at the different time samples for correct and incorrect solutions conditions and (B) full time-frequency power plots of the difference between Incorrect and Correct solutions. Top row in both panels shows the results of the TD group and the bottom row shows the Alcohol-Exposed group. Note the relative increases in the power of 6–7 Hz frequencies bands for the Incorrect condition compared to the Correct one in the TD infants but not in the Alcohol-Exposed infants. (C) Topographic distribution of the correlations between the 6–7 Hz power difference between Incorrect and Correct solutions and prenatal exposure to alcohol (mean oz absolute alcohol per occasion). (D) Mean 6–7 Hz power for each condition for each participant group.

power difference between the correct and incorrect conditions was inversely related to the amount of alcohol consumed per drinking occasion, both at the time of conception and during pregnancy. The latter finding is consistent with evidence from animal model studies that adverse effects of prenatal alcohol exposure are often more severe when animals are exposed to concentrated binge-like doses of ethanol than when larger total quantities of alcohol are administered gradually in smaller doses over a more extended period (e.g., (Bonthuis and West, 1990)). The very heavy maternal alcohol consumption binge pattern of drinking in this sample clearly played a critical role in the effect seen on the neurophysiological outcomes. It is important to note that, by contrast to the original Wynn behavioral version, our ERP measures are also able to reveal a specific deficit in error detection in FASD infants. Moreover, it is notable that the effects of PAE observed in this study were not attributable to SES, maternal education, prenatal exposure to smoking, infant’s age at testing, or any of the other control variables that were either adjusted statistically in the data analysis or found to be unrelated to the infant outcomes.

Our finding that infants with PAE fail to detect the errors in the arithmetical equations provides evidence of a very specific deficit in cognitive function early in development that can be detected early using

this ERP paradigm. Two different mechanisms may account for this deficit. The alcohol-exposed infants may be delayed in developing ACC-mediated error monitoring. Although, to our knowledge, error monitoring has not been specifically examined in studies of children and adults with PAE, there is extensive evidence of deficits in aspects of executive function that depend, at least in part, on error monitoring (Mattson et al., 1999; Olson et al., 1998). In addition, given that error detection constitutes a critical element of information processing generally, it seems likely that this early deficit plays an important role in the other cognitive delays seen in children with prenatal alcohol exposure.

Alternatively, the deficit in error detection in this study may be attributable to fetal alcohol-related impairment in the brain circuitry mediating number processing (i.e., the IPS and related areas). In an fMRI study conducted in Cape Town, school-age children with FAS and PFAS failed to recruit the classic circuitry involved in magnitude comparison and simple addition (Meintjes et al., 2010). Moreover, a continuous measure of maternal alcohol consumption during pregnancy was related to lower levels of activation in the right IPS in both tasks (magnitude comparison and simple addition), $r_s = -0.37$ and -0.40 , both $p_s < 0.01$, respectively (Woods et al., 2015). Similarly, in an Atlanta sample,

prenatally exposed young adults with fetal alcohol-related dysmorphic features who were given a subtraction task showed lower levels of activation in parietal regions known to be associated with arithmetic processing when compared with TD adults (Santhanam et al., 2009). Thus, the failure of the alcohol-exposed infants to detect the errors in the present study may be attributable to fetal alcohol-related impairment in the neural circuitry that mediates number processing, thereby limiting the infants' ability to derive the expectation about the correct solution. In ongoing ERP studies with adolescents, we are currently examining the degree to which fetal alcohol-related number processing impairment later in development is attributable to specific deficits in error detection and/or in the neural circuitry that mediates number processing. To determine whether this deficit is due to developmental delay or constitutes a permanent deficit can be addressed in a future longitudinal study, in which this functional deficit is also assessed at a later point in development.

Author contribution

AB, SJ, and JJ designed the study and obtained an NIH/National Institute on Alcohol Abuse and Alcoholism grant to conduct the study. They collaborated in the implementation of the study, the data collection and analysis, and interpretation and write-up of the findings for publication. NL and CL collected the infant ERP data. MS and SL analyzed the ERP data and contributed to the writing of the manuscript. MS and ND assisted in the analysis of the data. CM and EM collaborated in the recruitment, diagnosis, and follow-up of the Cape Town longitudinal sample.

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Declaration of Competing Interest

We declare that the authors have no conflicts of interest to disclose.

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