Prenatal Alcohol Exposure Alters Error Detection During Simple Arithmetic Processing: An Electroencephalography Study

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Background: Arithmetic is the domain of academic achievement most consistently related to prenatal alcohol exposure (PAE). Error detection, an important aspect of arithmetic processing, can be examined in a mathematical verification task. Electroencephalographic (EEG) studies using such tasks have shown bursts of synchronized theta-band activity in response to errors. We assessed this activity for error detection in adolescents with PAE and typically developing (TD) matched controls. We predicted that the PAE group would show smaller theta bursts during error detection and weaker responses depending on the size of the error discrepancy.

Methods: Participants' mothers were recruited during pregnancy and interviewed about their alcohol consumption using a timeline follow-back interview. Participants were followed from infancy and diagnosed for fetal alcohol syndrome (FAS) or partial FAS (PFAS) by expert dysmorphologists. EEGs were recorded for 48 adolescents during a verification task, which required differentiation between correct/incorrect solutions to simple equations; incorrect solutions had small or large deviations from correct solutions.

Results: Performance was good–excellent. The PAE group showed lower accuracy than the TD group: Accuracy was inversely related to diagnosis severity. The TD and heavily exposed (HE) nonsyndromal groups showed the expected differentiation in theta-burst activity between correct/incorrect equations, but the FAS/PFAS groups did not. Degree of impairment in brain response to errors reflected severity of diagnosis: The HE group showed the same differentiation between correct/incorrect solutions as TD but failed to differentiate between levels of discrepancy; PFAS showed theta reactions only in response to large error discrepancies; and FAS did not respond to small or large discrepancies.

Conclusions: Arithmetical error–related theta activity is altered by PAE and can be used to distinguish between exposed and nonexposed individuals and within diagnostic groups, supporting the use of numerical and quantitative processing patterns to derive a neurocognitive profile that could facilitate diagnosis and treatment of fetal alcohol spectrum disorders.

Key Words: Prenatal Alcohol Exposure, Fetal Alcohol Spectrum Disorders, Fetal Alcohol Syndrome, Electroencephalography, Numerical Processing, Error Detection.

FETAL ALCOHOL SPECTRUM disorders (FASD) is an umbrella term covering a range of disorders related to prenatal alcohol exposure (PAE). Fetal alcohol syndrome (FAS), the most severe of the disorders, is characterized by a distinctive set of facial anomalies (short palpebral fissures, thin upper lip, flat philtrum), microcephaly, and pre- or postnatal growth restriction (Hoyme et al., 2005). This craniofacial dysmorphology is also seen in partial FAS, together with microcephaly, growth restriction, or neurobehavioral deficits. In alcohol-related neurodevelopmental disorder (ARND), the most prevalent FASD, prenatally exposed children exhibit significant cognitive and/or behavioral impairment but do not meet criteria for the FAS or PFAS. PAE has been linked to a broad range of cognitive and behavioral problems, including deficits in executive function (EF; Connor et al., 2000; Vaurio et al., 2010), attention and memory (Coles et al., 1997; Lewis et al., 2015; Mattson and Roebuck, 2002), eyeblink conditioning (Jacobson et al., 2011b, 2008), information processing speed (Burden et al., 2005; Jacobson et al., 1993; Streissguth et al., 1994), and lower IQ (Jacobson et al., 2004; Streissguth et al., 1994).

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Arithmetic is the domain of academic achievement most strongly and consistently related to fetal alcohol exposure (Glass et al., 2017; Jacobson et al., 2011a, 2011b; Santhanam et al., 2009). Arithmetic deficits are found in both calculation and estimation tests (Kopera-Frye et al., 1996), with performance on arithmetic tests more impaired than reading or spelling (Howell et al., 2005; Kerns et al., 1997). PAE is related to poorer performance in all 3 of these domains, but only the effects on arithmetic remain significant after statistical adjustment for IQ (Goldschmidt et al., 1996; Jacobson et al., 2011a).

Recent evidence from behavioral and neuroimaging studies has linked PAE to a deficit in the core quantity system identified by Dehaene and associates (Dehaene, 1992; Dehaene and Cohen, 1995), resulting in an impaired ability to mentally represent and manipulate numbers and quantities (Jacobson et al., 2011a; Santhanam et al., 2009). For example, in an fMRI study involving magnitude comparison and simple arithmetic, higher levels of PAE were associated with lower levels of activation in a region of the intraparietal sulcus (IPS) known to mediate quantity processing (Woods et al., 2008).

An important aspect of arithmetic processing that has not yet been examined in relation to PAE relates to error detection, which can be assessed in a mathematical verification task. In this type of task, the subject is asked to judge the correctness of a mathematical problem or equation. Presentation of an incorrect equation (e.g., $2 + 2 = 5$) has been found to evoke a clear pattern of brain activity (Avancini et al., 2015), consisting of a burst of synchronized theta-band activity recorded using electroencephalography (EEG; Tzur et al., 2009). This theta-band activity, which has been localized to the anterior cingulate gyrus (ACC; Luu et al., 2003), appears to reflect a violation of expectations emanating from the comparison between expected and perceived stimuli (Tzur and Berger, 1993). Detection of erroneous information by the ACC is not domain-specific and seems to be triggered by information flow from domain-specific brain areas, with the ACC making the comparisons and signaling when a violation of expectations is detected (Alexander and Brown, 2011; Shenhav et al., 2013). For linguistic information, the initial information flow comes from areas dedicated to language; for numerical information, from the IPS (e.g., Kaufmann et al., 2005). In the arithmetical domain, these theta bursts have been found to increase as a function of the degree of disparity between the correct solution in a mathematical equation and the displayed erroneous solution (Tzur et al., 2009).

In the present study, we assessed the theta-burst brain activity signature for error detection to erroneous arithmetical equations in a sample of adolescents with heavy PAE and typically developing (TD) age- and community-matched controls. These adolescents were born to women prospectively recruited and interviewed during pregnancy, who provided detailed information regarding their alcohol consumption at that time. The participants were then followed longitudinally from infancy through adolescence.

Based on the prior evidence of arithmetic impairment in FASD, we predicted that the alcohol-exposed children would show (i) smaller theta bursts during error detection than the controls and (ii) a weaker response as a function of the size of the error discrepancy (Tzur and Berger, 2007). (iii) We also predicted that the severity of this impairment would be related to diagnosis, with the strongest effects seen in the adolescents with FAS, followed by those with PFAS and then by those who were heavily exposed (HE) but nonsyndromal. Continuous measures of PAE were also used to examine the degree to which the observed effects were dose-dependent.

MATERIALS AND METHODS

Participants

This study was conducted in Cape Town, South Africa, where the prevalence of FASD in the Cape Coloured (mixed ancestry) community is among the highest in the world (13.6 to 20.9%) and where the incidence of FAS has been estimated to be 18 to 141 times greater than in the United States (May et al., 2013). This population, composed of descendants of white European settlers, Malaysian slaves, Khoi-San aboriginals, and black Africans, has historically comprised the majority of workers in the wine-producing region of the Western Cape. The prevalence of FAS in this community is a consequence of very heavy maternal drinking during pregnancy (Croxford and Viljoen, 1999), which, in turn, is due in part to poor psychosocial circumstances and the traditional *dop* system, whereby farm laborers were paid, in part, with wine. Although the *dop* system has been outlawed and despite numerous efforts to reduce pregnancy drinking, weekend binge drinking persists in a high proportion of women during pregnancy in rural and urban Cape Coloured communities (May et al., 2013).

The sample consisted of 50 (25 TD, 25 heavily alcohol exposed) Cape Coloured adolescents from our Cape Town Longitudinal Cohort (Jacobson et al., 2008). Due to the high level of comorbidity of attention deficit/hyperactivity disorder (ADHD) in FASD (Fryer et al., 2007), 50 adolescents meeting research criteria for ADHD (Jacobson et al., 2011a) were excluded from this sample. Participants were born to women recruited at their initial visit to an antenatal clinic serving an economically disadvantaged, predominantly Cape Coloured population (Jacobson et al., 2008). A research nurse interviewed each mother at her first antenatal visit using the "gold standard" timeline follow-back procedure (TLFB; Jacobson et al., 2002) regarding her alcohol consumption both at the 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/d) or engaging in binge drinking ($\geq$5 drinks/occasion) was invited to participate in the study. Women who abstained or drank only minimally were recruited as controls (all but 1 control abstained; she consumed low levels of alcohol: <1 to 2 drinks on 3 occasions $\approx$ 0.01 oz AA/d). Exclusionary criteria were maternal age <18 years of age, HIV infection, or those with diabetes, epilepsy, or cardiac problems requiring treatment. Infant exclusionary criteria were major chromosomal anomalies, neural tube defects, multiple births, or seizures.

At follow-up visits in mid-pregnancy and at 1 month postpartum, the TLFB interview was readministered to obtain information about the mother's drinking during the previous 2 weeks and during the latter part of pregnancy, respectively. Data from the 3 interviews provided 3 continuous measures of alcohol exposure: oz AA/d, alcohol dose/occasion (AA drinking/occasion), and frequency of alcohol use (d/wk). Mothers were also interviewed regarding their smoking (cigarettes/d) and illicit drug use (marijuana, methamphetamine ("tik"), cocaine, heroin, and methaqualone ("mandrax"; days/month)) during pregnancy.

In September 2005, each child was examined for alcohol-related anomalies and growth in a neighborhood clinic by 2 U.S.-based expert dysmorphologists (H.E. Hoyme and L.K. Robinson) using a standard diagnostic protocol (Hoyme et al., 2005; Jacobson et al., 2008). There was substantial interexaminer agreement on the assessment of the principal fetal alcohol-related dysmorphic features between the 2 dysmorphologists (Jacobson et al., 2008). Case conferences including the dysmorphologists, SWJ, JLJ, and CDM were held to reach consensus regarding diagnosis of FAS and PFAS. Those who did not meet criteria for FAS or PFAS were categorized as HE nonsyndromal. The children were reexamined in FASD clinics by expert dysmorphologists held in 2009, 2013, and 2016, in which Dr. Hoyme was the lead dysmorphologist. Dr. Hoyme subsequently reviewed the diagnoses from all 4 assessments in a case conference with SWJ and JLJ at which they assigned a final diagnosis to each participant.

Of the 50 adolescents, 2 (4%) did not complete the EEG assessment; data were, therefore, analyzed for the remaining 48. The TD group consisted of 23 participants (12 males); the exposed group, of 25 participants: 9 nonsyndromal HE (6 males); 8 PFAS (4 males); and 8 FAS (3 males). Although these 25 participants were recruited prenatally into a single exposed group, we examine them here as 3 separate groups in order to examine diagnosis-related differences. All participants completed at least 6 years of formal education. Demographic background characteristics for the sample are presented in Table 1. There were no sex or age effects related to EEG assessment. Not surprisingly, IQ was higher in the TD and HE than in the FAS and PFAS groups.

Procedure

We used a computerized equation verification task adapted from Tzur and Berger (2007, 2009) and Tzur et al. (2010). After 8 practice trials, each participant was presented with 240 trials of simple mathematical equations (addition or subtraction), which were followed by either a correct (50% trials) or incorrect solution (50% trials). Within the incorrect solution condition, there were 2 levels of discrepancy—1 or 5—appearing with equal probability. For example, for the equation "1 + 2 =," the incorrect solution could be either "4" (L1; i.e., discrepant from the correct solution by 1) or "8" (L5; i.e., discrepant from the correct solution by 5; see Fig. 1). The number of positive and negative incorrect solutions was also equal. None of the equations included identical operands (e.g., 3 + 3, 4 + 4). The 240 trials were presented in a random order within 10 blocks (24 correct and incorrect trials in each block).

Each trial began with a fixation point (500 ms), followed by an equation (1,500 ms), then a black screen (400/500/600 ms—for baseline calculation, see below), followed by a solution (1,500 ms) (Fig. 1). After the solution, a screen presenting a question mark appeared, until a response was given. Participants were instructed to distinguish between correct and incorrect solutions by pressing one button if the solution was correct; a second button, if it was incorrect. The participant was instructed to delay pressing the button until the question mark appeared to ensure that motor activity (i.e., the button press) would not coincide (overlap) with the neural activity generated during the evaluation of the presented solution. Participants were asked to respond only when they were confident of their decisions and not as quickly as possible.

Three behavioral outcome measures were generated: percent of correct solutions correctly identified (Crr), percent of incorrect solutions differing by 5 correctly identified (L5), and percent of equations with incorrect solutions differing by 1 correctly identified (L1).

IQ was assessed on the Wechsler Abbreviated Scale of Intelligence (WASI). Math achievement was assessed on the Numerical Operations and Mathematical Reasoning subtests of the Wechsler Individual Achievement Test (WIAT).

Table 1. Sample Characteristics

	TD (n = 23)	HE (n = 9)	PFAS (n = 8)	FAS (n = 8)	F or χ^2	Post hoc differences[a]
Maternal characteristics						
Age at delivery	26.1 (4.5)	24.7 (5.3)	24.4 (4.2)	34.1 (5.0)	8.01***	FAS > TD, HE, PFAS
Education (years)	9.8 (1.7)	9.7 (2.8)	7.4 (2.0)	8.1 (1.8)	3.91*	TD > PFAS
Socioeconomic status[b]	25.1 (8.2)	17.9 (5.9)	13.2 (4.9)	16.3 (6.8)	7.20***	TD > PFAS, FAS
Marital status (% married)	47.8	11.1	0.0	25.0	8.66*	TD > PFAS
Prenatal exposure						
oz AA/d	0.0004 (0.002)	1.1 (0.8)	1.0 (0.6)	2.0 (2.3)	8.47***	HE, FAS > TD
oz AA/drinking day	0.1 (0.2)	4.7 (4.2)	3.4 (1.2)	5.1 (1.6)	20.62***	HE, PFAS, FAS > TD
Frequency (d/wk)	0.003 (0.01)	1.7 (0.8)	2.0 (0.7)	2.2 (1.9)	20.77***	HE, PFAS, FAS > TD
Cigarettes/d	1.8 (4.4)	4.7 (4.9)	10.1 (7.5)	6.8 (6.5)	5.13**	PFAS > TD
Marijuana (d/mo)	0.1 (0.4)	1.0 (2.4)	0.0 (0.0)	0.0 (0.0)	2.14	
Adolescent characteristics						
Completed school grade	9.9 (1.1)	8.6 (1.7)	8.8 (1.3)	8.4 (1.9)	4.15*	TD > FAS
Age at EEG assessment	16.2 (0.8)	16.0 (0.7)	16.6 (0.8)	16.4 (0.8)	1.03	
Sex (% male)	52.2	66.7	50.0	62.5	1.46	
WASI IQ[c]	84.3 (13.3)	82.8 (12.6)	68.9 (9.8)	67.9 (10.3)	5.69**	TD > PFAS, FAS
WIAT[d]						
Mathematical Reasoning	78.2 (16.0)	79.6 (12.6)	67.3 (15.7)	62.5 (16.7)	2.87*	
Numerical Operations	74.1 (18.4)	76.1 (17.7)	62.3 (12.2)	57.5 (16.5)	2.76†	

Values are Mean (SD).
EEG, electroencephalography; FAS, fetal alcohol syndrome; PFAS, partial FAS; TD, typically developing.
[a] $p < 0.05$, using pairwise post hoc Tukey tests; marital status: Fisher's exact test.
[b] Hollingshead Scale (2011).
[c] Wechsler Abbreviated Scale of Intelligence.
[d] Wechsler Individual Achievement Test.
† $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

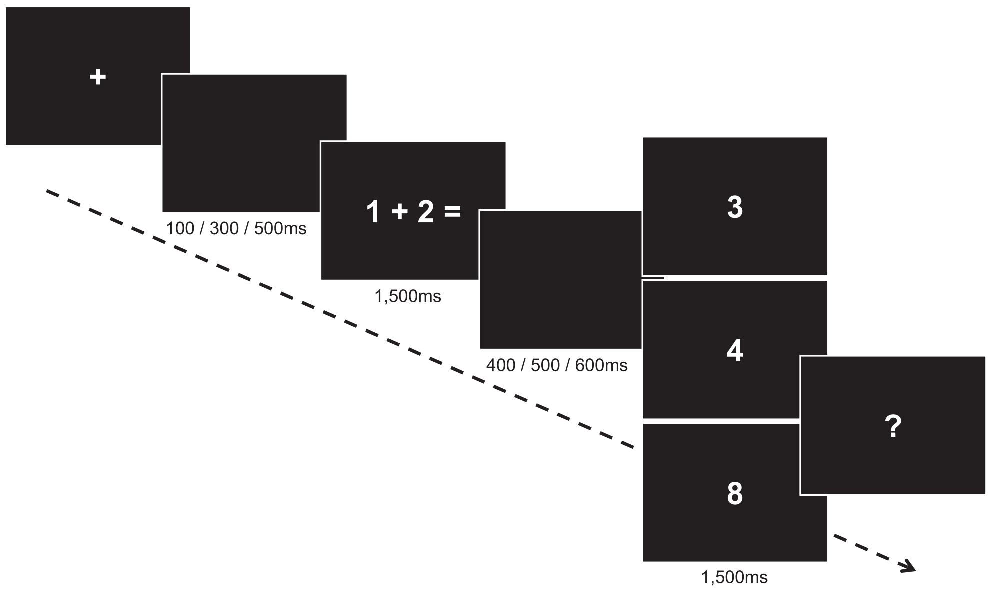

Fig. 1. Sample trial from the computerized equation verification task. In each trial, participants were presented with a simple equation (see above; "1 + 2 =") followed by a delayed possible solution. The solution could be correct (e.g., "3") or incorrect by a deviation of 1 (L1; e.g., "4") or by a deviation of 5 (L5; e.g., "8"). The delay between the onset of the equation and solution was designed to allow participants sufficient time to solve the equation before the solution appeared. Electroencephalography segmentation was locked to the solution presentation onset, and participants withheld their responses until prompted by the appearance of a question mark

EEG Recording

EEGs were recorded using an EGI HydrocCel Geodesic Sensor Net (HCGSN) and system (Electrical Geodesics, 2003). A total of 129 electrodes were distributed on the scalp according to an adapted 10 to 20 method and were sampled at a rate of 250 Hz (Tucker, 1990). Recording frequency band was constant at 0.01 to 100 Hz. The electrode impedance level was kept under 40 KΩ, which is an acceptable level for this system (Ferree et al., 2001). During EEG recording, all measures were referenced to an electrode located above Cz (according to the 10 to 20 method).

EEG Preprocessing

Preprocessing was performed using the EEGLAB toolbox (version 14; Delorme and Makeig, 2004) operating in the MATLAB environment (version 2017a). Continuous EEG data were first high-pass-filtered offline at 0.5 Hz and rereferenced to the average of the channels across the scalp. The continuous data were segmented into epochs starting 400ms before and ending 700ms after the stimulus onset (stimulus-locked). To avoid edge artifacts resulting from complex wavelet convolution (explained below), 2-sec buffer zones were added to the beginning and end of each segment, resulting in segments starting 2,400ms before and ending 2,700ms after stimulus onset. Segmented data were then baseline-corrected by subtracting the mean amplitude based on a 400-ms-long period pre–stimulus onset. Trials with incorrect responses were excluded from further analysis.

Epoched data were visually inspected, and trials containing large artifacts, and faulty channels were manually removed. Next, an independent component analysis (ICA) was conducted using EEGLAB's runica algorithm. Components containing blinks, oculomotor artifacts, or other artifacts that could be clearly distinguished from genuine neural activity signals were subtracted from the data. Finally, the data were subjected to an automated bad-channel and artifact detection, followed by manual verification. Bad channels were spherically interpolated based on activity from neighboring channels. EEG preprocessing was performed by an experimenter who was blinded to participants' grouping and experimental condition.

Time–Frequency Analysis

Single-trial data were decomposed into their time–frequency representation using custom scripts and functions written in MATLAB. The power spectrum of the EEG was multiplied by the power spectrum of complex Morlet wavelets (Cohen, 2014): $e^{i2\pi tf} \times e^{2/\sigma^2}$, 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 30 Hz in 1 Hz steps, while σ was set according to $n/2\pi f$, where n increased from 3 to 10 to maintain a fair balance between temporal and frequency resolution. Following convolution, the inverse fast Fourier transform was taken to reshape data back into individual epochs. Edge artifacts were confined to 2-s-long buffer zones at both ends of each epoch.

From the resulting complex signal, trial-averaged power values were computed. Power was then normalized relative to the average power during a prestimulus baseline period at each frequency band for each participant and condition for all the electrodes. Since temporal smoothing from time–frequency decomposition can falsely introduce trial-related activity into the immediate prestimulus time period, the baseline period was defined as the period ranging from 400 to 200 ms prestimulus (Cohen, 2014, pp. 230–234). Mean event-related spectral perturbations (ERSP) power in each of the frequency bands was measured for each participant and condition, based on a group of 8 channels around Fz (see Fig. 2*A*) in a time window of 160 to 410 ms post–stimulus onset, which capture the theta effects seen in the time-by-frequency plot (Fig. 2*B* below) and are compatible with theta effects reported in error detection and evaluation tasks (Cohen et al., 2007; Tzur and Berger, 2007). Mean power was measured in the delta (1 to 3 Hz), theta (4 to 7 Hz), alpha (8 to 12), and beta (13 to 30) frequency bands. Following previous findings (Conejero et al., 2018), where the effect of correctness was found within a finer theta band, the theta band was broken into low theta (4 to 5 Hz) and high theta (6 to 7 Hz), resulting in a total of 5 frequency bands.

Statistical Analysis

All statistical analyses and plotting were conducted in R (R Core Team, 2018), using the packages described below. Because participants were instructed to delay their button presses until after the question mark was displayed (Fig. 1) to prevent confounding of arithmetic processing with motor response, the behavioral analysis focused on response accuracy only and not response times.

The following control variables were examined: participant sex, age at EEG recording, and completed school grade, and mother's years of education, smoking (cigarettes/d) and marijuana use (d/mo) during pregnancy, socioeconomic status (SES), and age at delivery. Pearson r was used to examine the relation of each control variable to each behavioral and EEG outcome measure (see Table 2 below). Any variable that was even weakly related to a given outcome ($p < 0.10$) was considered a potential confounder of the effect of PAE on that outcome. Confounders were controlled for in the analysis of the behavioral and EEG outcomes by including them as covariates in the analyses of covariance (ANCOVAs).

Mean accuracy was analyzed using a repeated-measures analysis of variance (ANOVA), with group (TD, HE, PFAS, FAS) as a between-subjects factor, and correctness as a within-subject factor. Theta power was analyzed using a repeated-measures ANOVA, with group (TD, HE, PFAS, FAS) as a between-subjects factor, and correctness and frequency as within-subject factors. Both ANOVAs were conducted using the afex R package (Singmann et al., 2018). All planned and post hoc comparisons and contrasts were conducted using the emmeans R package (Lenth, 2018).

RESULTS

Behavioral Results

Accuracy was analyzed using a mixed ANCOVA with correctness as a within-subject variable, group (TD, HE, PFAS, and FAS) as a between-subjects variable, and completed school grade as a covariate, as it was positively related to a greater overall accuracy rates (Table 2). The analysis of the accuracy levels revealed a main effect for Correctness, $F(2, 86) = 8.96$, $p < 0.001$, $\eta_p^2 = 0.17$, in which accuracy for Correct was smaller than for Incorrect equations {L1 + L5}, $t(43) = -3.42$, $p < 0.001$, $\eta_p^2 = 0.21$, and greater for L5 compared to L1 equations, $t(43) = -2.39$, $p = 0.021$, $\eta_p^2 = 0.12$ (see Table 3).

Accuracy for all 4 diagnostic groups was relatively high: Average accuracy was 92%, and accuracy was above 80% even in the most challenging conditions and more impaired groups (Table 3). Nevertheless, there was a main effect for Group, $F(3, 43) = 2.88$, $p = 0.046$, $\eta_p^2 = 0.17$. Planned

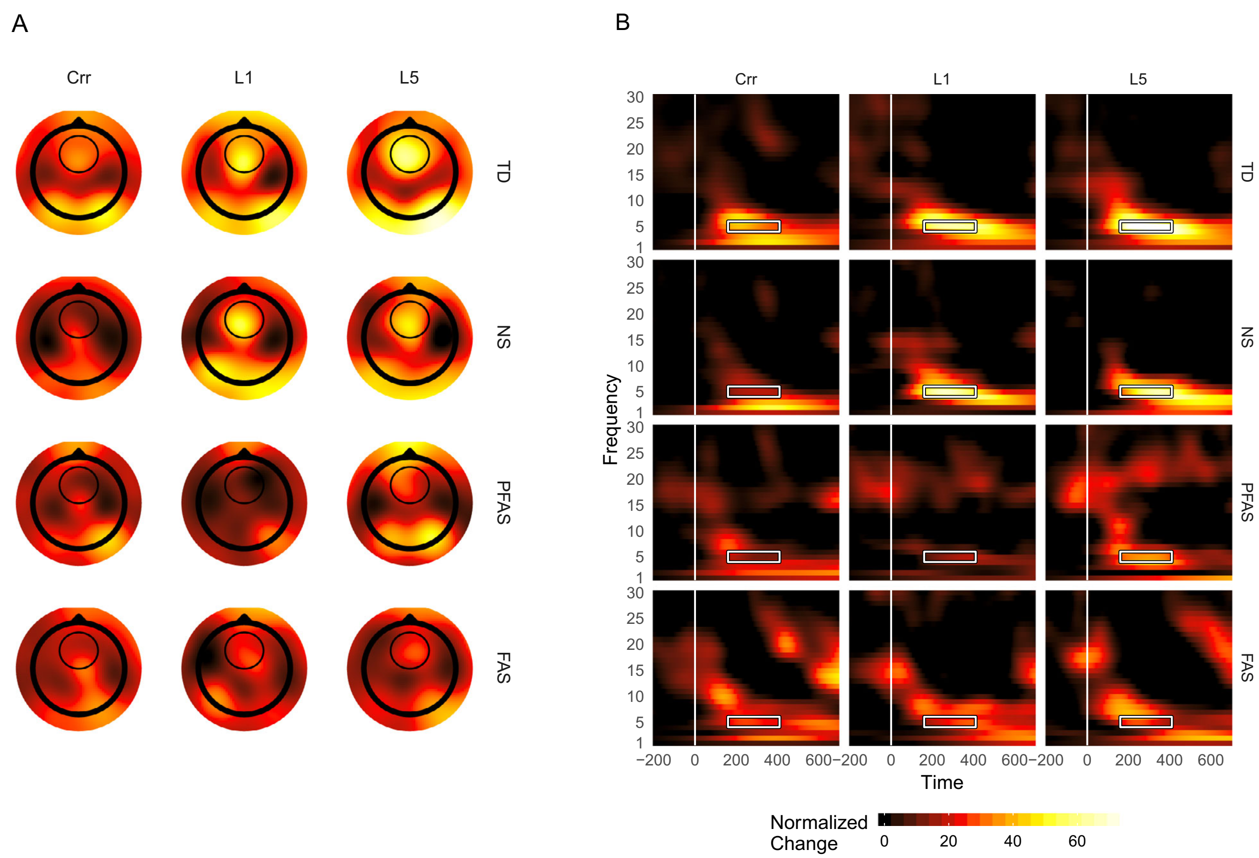

Fig. 2. ERSP (event-related spectral perturbations) power for all groups (rows) and conditions (columns). (**A**) Topographical maps of low theta (4 to 5 Hz) ERSP power in the 160- to 410-ms poststimulus time window. The small circle indicates the group of 8 channels from which mean ERSP was measured. (**B**) Time-by-frequency plot, as measured from a group of 8 frontal channels. The white vertical line marks the stimulus onset, and the white box indicates the 160- to 410-ms poststimulus time window and the low theta (4 to 5 Hz) frequency band in which mean power was measured

Table 2. Correlation of Background Variables with Behavioral and EEG Outcomes (N = 48)

	Accuracy		EEG measures	
	Mean accuracy	Discrepancy (L5 – L1)	Error detection (L – Crr)	Discrepancy (L5 – L1)
Participant characteristics				
Sex (male)	0.18	0.17	−0.06	−0.06
Age at EEG assessment	0.05	−0.14	−0.22	0.07
WASI IQ[a]	0.40**	−0.22	0.22	0.06
Completed school grade	0.41**	−0.14	0.04	0.22
Maternal characteristics				
Age at delivery	−0.10	0.00	−0.15	−0.08
Education (years)	0.03	−0.11	0.27†	0.14
Socioeconomic status[b]	−0.04	−0.08	0.10	0.21
Marital status	−0.17	−0.21	0.00	−0.05
Prenatal exposure				
Cigarettes/d	0.09	0.17	−0.01	−0.06
Marijuana (d/mo)	0.00	0.17	−0.11	−0.03

Values are Pearson r.
EEG, electroencephalography.
[a]Wechsler Abbreviated Scale of Intelligence.
[b]Hollingshead Scale (2011).
†p < 0.10, *p < 0.05, **p < 0.01, ***p < 0.001.

Table 3. Means (Standard Deviations) of the Behavioral and EEG Outcomes by Diagnostic Groups (N = 48)

	TD	HE	PFAS	FAS
Accuracy				
Crr	97.0% (3.1%)	96.2% (4.0%)	87.8% (9.7%)	83.4% (20.2%)
L1	96.8% (4.9%)	97.0% (4.3%)	92.6% (11.9%)	84.3% (21.3%)
L5	98.2% (2.3%)	97.8% (3.7%)	96.1% (5.7%)	86.0% (20.7%)
Theta ERSP				
Crr	34.0 (23.8)	19.2 (19.7)	17.3 (15.1)	20.9 (20.1)
L1	50.4 (28.0)	56.3 (38.1)	14.2 (13.1)	20.4 (16.9)
L5	74.8 (61.3)	48.0 (55.7)	37.7 (27.8)	20.0 (26.0)

EEG, electroencephalography; FAS, fetal alcohol syndrome; HE, heavily exposed; PFAS, partial FAS; TD, typically developing

comparisons showed that the HE and TD groups showed similar accuracy rates, $d = 2.6\%$, $t(43) = 0.71$, $p = 0.483$, $\eta_p^2 = 0.01$. Moreover, within the 3 exposed groups there was a linear trend: The more severe the diagnosis, the poorer the performance, $t(43) = 2.79$, $p = 0.008$, $\eta_p^2 = 0.15$. The quadratic trend was not significant.

There was also a marginal interaction between Group and Correctness, $F(6, 86) = 2.15$, $p = 0.056$, $\eta_p^2 = 0.13$. Further analysis of this interaction by polynomial contrasts between the groups for each level of correctness showed that the overall pattern in the different conditions was similar, although the size and strengths of these effects differed between the conditions: In the Correct condition, the HE and TD groups did not differ in their accuracy rates, $d = 2.8\%$, $t(43) = 0.77$, $p = 0.446$, $\eta_p^2 = 0.01$, with a significant linear trend within the exposed groups, $t(43) = 2.86$, $p = 0.006$, $\eta_p^2 = 0.16$. In the L1 Incorrect condition, the HE and TD groups showed similar accuracy rates, $d = 3.2\%$, $t(43) = 0.74$, $p = 0.462$, $\eta_p^2 = 0.01$, with a linear trend within the exposed groups, $t(43) = 2.49$, $p = 0.017$, $\eta_p^2 = 0.13$. In the L5 Incorrect condition, the HE and TD groups showed similar accuracy rates, $d = 1.9\%$, $t(43) = 0.52$, $p = 0.606$, $\eta_p^2 < 0.01$, with a linear trend within the exposed groups, $t(43) = 2.74$, $p = 0.006$, $\eta_p^2 = 0.15$. No quadratic trends within the exposed groups were found for any of the conditions (all $ps > 0.324$, $\eta_p^2 < 0.02$).

The behavioral outcomes were examined in relation to performance on the Numerical Operations and Mathematical Reasoning subtests from the WIAT, the participants' IQ scores, and to the measures of PAE. Not surprisingly, overall accuracy on this task was related to both Numerical Operations, $r(47) = 0.54$, $p < 0.001$, and Mathematical Reasoning, $r(47) = 0.58$, $p < 0.001$, as well as to IQ scores, $r(47) = 0.40$, $p = 0.005$. Likewise, a smaller discrepancy in accuracy between the L1 and L5 conditions was also related to Numerical Operations, $r(47) = -0.33$, $p = 0.022$, and Mathematical Reasoning, $r(47) = -0.30$, $p = 0.042$, but not to IQ scores, $r(47) = -0.22$, $p = 0.134$. However, neither of the behavioral outcomes was related to any of the PAE measures ($r(47) < |0.19|$, $p > 0.191$).

Time–Frequency Results

The data for the TD group were initially analyzed using repeated-measures ANOVA to determine the frequency range within which the theta bursts differed in response to error detection in this sample. Five frequency bands were examined: delta (1 to 3 Hz), low theta (4 to 5 Hz), high theta (6 to 7 Hz), alpha (8 to 12 Hz), and beta (13 to 30 Hz). There was a main effect for frequency band, $F(4, 88) = 33.06$, $p < 0.001$, $\eta_p^2 = 0.60$, with the highest ERSP in the low theta bands. There was also a main effect for correctness, $F(4, 44) = 3.39$, $p = 0.043$, $\eta_p^2 = 0.13$, with the highest ERSP in response to the incorrect L5 solutions and the lowest in response to the correct solutions. Moreover, as expected, there was a significant frequency $\times$ condition interaction, $F(8, 176) = 4.74$, $p < 0.001$, $\eta_p^2 = 0.18$, such that the effect for correctness was significant only within the low theta (4 to 5 Hz) band, $F(2, 22) = 7.454$, $p = 0.003$, $\eta_p^2 = 0.40$, and not in any of the other bands (all $ps > 0.174$).

We next examined the differences in the effects of correctness between the alcohol exposure groups (i.e., the interaction between correctness and exposure group) within the 4- to 5-Hz band. Since mothers' education was positively related to a greater difference in theta-burst magnitude between the correct and the incorrect conditions (Table 2), mothers' education (centered at 0) was entered as a covariate in the following ANCOVA. Mean power was analyzed using a mixed ANCOVA with correctness as a within-subject variable, group (TD, HE, PFAS, and FAS) as a between-subjects variable, and mothers' education as a covariate.

The ANCOVA revealed a main effect for correctness, $F(2, 86) = 5.93$, $p = 0.004$, $\eta_p^2 = 0.12$, and a marginally significant main effect for group, $F(3, 43) = 2.72$, $p = 0.056$, $\eta_p^2 = 0.16$. Although the interaction between group and correctness was not significant, likely due to the relatively small size of the subgroups, $F(6, 86) = 1.40$, $p = 0.223$, $\eta_p^2 = 0.09$, we examined whether the patterns of error detection (increased theta power for L1 and L5 compared to correct solutions) and of discrepancy (increased theta power for L5 compared to L1) differed between the groups (Table 3). These 2 effects were tested within each group using 1-tailed planned comparison contrasts.

The expected effect for error detection (increased theta power for L1 and L5 compared to correct solutions) was found within the TD group, $t(43) = 3.64$, $p < 0.001$, $\eta_p^2 = 0.24$, and the HE group, $t(43) = 2.76$, $p < 0.001$, $\eta_p^2 = 0.15$, but not within the PFAS or FAS groups (both $ps > 0.157$, $\eta_p^2 < 0.02$). When comparing the size of this difference between the 3 exposed groups using polynomial contrasts, a marginally significant linear trend was found, $t(43) = -1.75$, $p = 0.087$, $\eta_p^2 = 0.07$, such that the HE group showed the largest difference, and FAS, the smallest difference (Figs 2 and 3). The expected discrepancy effect (increased theta power for L5 compared to L1) was found for the TD group, $t(43) = 2.18$, $p = 0.018$, $\eta_p^2 = 0.10$, and the PFAS group, $t(43) = 1.71$, $p = 0.047$, $\eta_p^2 = 0.06$, but not within the HE or FAS groups ($p > 0.256$, $\eta_p^2 < 0.01$). When comparing the size of this difference between the 3 exposed groups using polynomial contrasts, a marginally significant quadratic trend was found , $t(43) = 1.69$, $p = 0.098$, $\eta_p^2 = 0.06$, such that the PFAS group showed a larger difference compared to the HE and FAS groups.

The EEG outcomes were examined in relation to performance on the Numerical Operations and Mathematical Reasoning subtests from the WIAT and the participants' IQ scores, and to the measures of PAE. While the effect for error detection was not related to Numerical Operations, Mathematical Reasoning, or IQ ($r(47) < x007C; .22x007C;$, $p > 0.126$), a decreased error detection effect was related to average oz AA consumed per day across pregnancy, $r(47) = -0.29$, $p = 0.049$, and marginally to frequency of alcohol use, $r(47) = -0.24$, $p = 0.095$.

DISCUSSION

In this study, we examined error detection accuracy and neural patterns of theta-burst activity in response to arithmetical errors in adolescents with and without heavy PAE and within the exposed group between adolescents differing in levels of severity of diagnosis. Behavioral performance

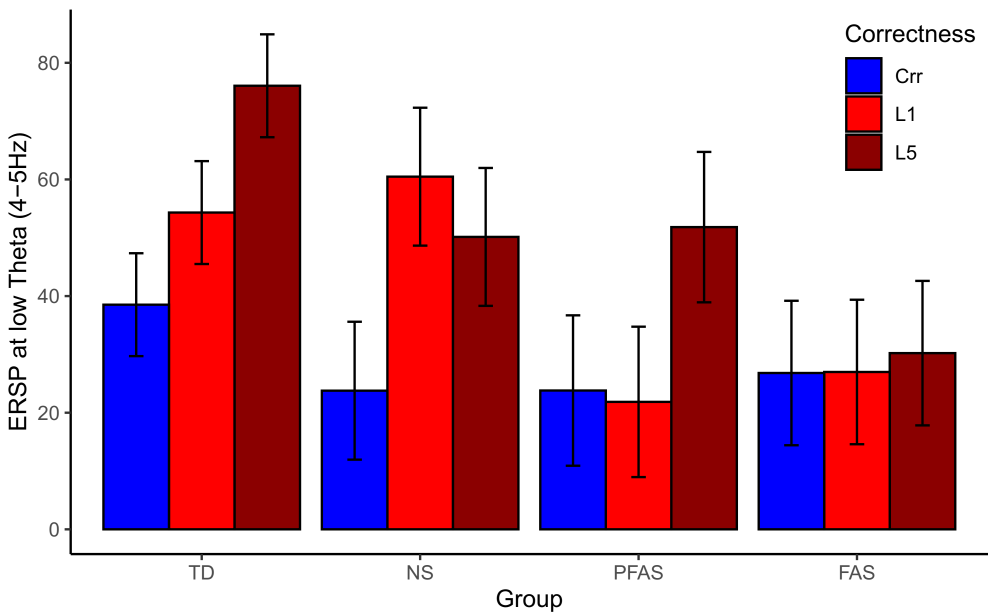

Fig. 3. Mean ERSP (event-related spectral perturbations) power at low theta (4 to 5 Hz) for each group and condition, controlling for mothers' education. Error bars denote standard errors

was generally good-to-excellent, as would be expected in a task requiring only very basic arithmetic proficiency and knowledge (i.e., determining correctness of single-digit addition or subtraction) in a sample of adolescents, all of whom had completed at least elementary school (6 years of formal education). Nevertheless, the alcohol-exposed participants performed more poorly than the TD group, and performance was inversely related to severity of diagnosis.

Our assessment of the neural activity elicited by the processing of erroneous arithmetical equations was based on previous literature indicating a specific neural response during perception of errors (Tzur and Berger, 2007) that is expressed in a theta frequency band signal, which has been localized to the ACC (Luu et al., 2003). Our results suggest differences in this neural reaction to the detection of arithmetical errors in the adolescents with and without heavy PAE, with differences in the error-related theta activity related to severity of diagnosis. Whereas the TD and nonsyndromal HE groups showed the expected theta burst in response to incorrect versus correct solutions, the FAS and PFAS groups did not exhibit this neural response. The HE group showed the normative differentiation between the correct and incorrect solutions seen in the TD group but failed to differentiate between degree of discrepancy (L1 vs. L5); the theta response in the PFAS group was seen only for the most discrepant incorrect solutions (i.e., L5), that is, extremely odd equations, such as $1 + 2 = 8$; and the FAS group showed no theta response in either condition.

It should be noted that even in the FAS group, in which the theta-burst brain signal was not detected at all, behavioral performance (i.e., accuracy) on the task was good enough to enable us to infer that their neural differences were not attributable to an inability to do the task. At the behavioral level, for an easy task, such as the one used here, adolescents could presumably rely on other neural processes, including working or long-term memory or other compensatory mechanisms to determine which solutions were correct. Reliance on alternative brain regions to compensate for inefficient processing in neural networks specialized for a given brain function has been reported extensively in the fMRI literature (see, e.g., Halperin and Schulz, 2006). For example, in the Cape Town cohort in which PAE was related to lower activation in the IPS during 2 simple arithmetic tasks (Woods et al., 2015), the syndromal children showed more extensive parietal activations (angular gyrus, posterior cingulate, and precuneus; Meintjes et al., 2010) and cerebellar activations that have been reported in adults only when more complex and rapid arithmetic processing is required (Menon et al., 2000). Similarly, in a study of working memory using a simple 1-back task, the TD group showed increased activity focused specifically in Broca's area, whereas the nonsyndromal HE group showed increased activity in an extensive fronto-striatal network usually activated for performing more challenging 2-back tasks, and those with FAS and PFAS showed increased activity in the parietal and cerebellar regions.

As previously noted, the theta-burst activity has been localized to the ACC and seems to reflect detection of a discrepancy between expected and perceived stimuli, situations, or actions by a general error monitoring process (Luu et al., 2003). Error monitoring is an important element in EF, a set of cognitive processes involved in selecting and monitoring behavior to facilitate attainment of chosen goals, which include cognitive inhibition, working memory, cognitive flexibility, and problem solving (Diamond, 2013). Frontal regions, including the ACC, dorsolateral prefrontal cortex, and orbitofrontal cortex, play critical roles in mediating EF. EF and frontal structural deficits have been extensively documented in FASD (Rasmussen, 2005; Sowell et al., 2018) although, to our knowledge, this is the first study to specifically examine the effect of PAE on error monitoring in adolescents. Our results presented here are consistent with our recently published findings in prenatally alcohol-exposed infants (Berger et al., 2019).

Error detection by the ACC is not domain-specific and results from information flow from domain-specific brain areas, with the ACC mediating the comparison processing and signaling when a violation of expectations is detected (Alexander and Brown, 2011; Shenhav et al., 2013). It is, therefore, possible that the pattern of results reported here is not attributable to a general deficit in ACC function but instead may reflect PAE-related impairment in brain areas specifically involved in quantitative processing that impedes or degrades incoming information flow to the ACC. Behavioral assessments reported in our Detroit Longitudinal PAE Cohort during adolescence indicated that the FASD-related impairment in arithmetic is mediated primarily by a specific deficit in magnitude comparison and not by poorer EF (Jacobson et al., 2011a) and, as noted, fMRI data from Cape Town have linked PAE to reduced recruitment of a region of the IPS that is specialized for quantitative processing (e.g., Woods et al., 2008). Similarly, in an fMRI study using a subtraction task, syndromal young adults with FASD showed less activation in the IPS and other math-related regions than nonsyndromal alcohol-exposed and control subjects (Santhanam et al., 2009). Our finding that error detection accuracy correlated more strongly with performance on standardized tests of math achievement than with overall IQ further supports the suggestion that the error detection deficit seen here may be related to impairment in the neural network specialized for number processing.

An additional point that should be noted is that the neurocognitive pattern displayed by the HE group in the current study also confirms previous work showing that HE shows an intermediate deficiency between PFAS and nonexposed individuals. An fMRI study found reduced activation in regions known to be associated with arithmetic processing (such as the IPS) in syndromal prenatally exposed adults, while nonsyndromal prenatally exposed adults showed intermediate activation that was not significantly different from the TD group (Santhanam et al., 2009). This pattern of results indicates that although nonsyndromal individuals

(HE group) suffer from some deficiency in automatic processing of symbolic numbers, the deficit is not as severe as that displayed by the PFAS groups, once again demonstrating the association between severity of diagnosis and quantitative processing.

Our study has several strengths. First, the mother's alcohol consumption was ascertained prospectively during pregnancy, providing a more reliable and valid assessment of degree of PAE (Jacobson et al., 2002). Second, the EEG assessment showed that a deficit in error detection constitutes an important element in the impairment in mathematical processing seen in FASD and provided evidence that the severity of this deficit is related to severity of FASD diagnosis. Moreover, the theta-burst data suggested that distinctively different patterns of functional brain deficits may mediate error detection in each of the 3 diagnostic groups, such that different remediation strategies may be appropriate. For the EEG data, we focused on a wavelet analysis, which provides a measurement of power in a given frequency regardless of phase. Whereas lower amplitude in a ERP wave can either indicate lower power in the underlying EEG signal or be due to phase jitter in the EEG signal between trials resulting in signal flattening in the average ERP wave (Luck, 2014, chap. 8), results from a wavelet analysis are not affected by latency or temporal jitter (Cohen, 2014, chap. 19). We can, therefore, infer that the observed effects of PAE reflect differences in specific neural activity rather than "noise" or less consistent activity.

There are also some limitations. Because the participants did not perform a nonquantitative verification task, we cannot determine the degree to which the observed deficit in error detection contributes to a general deficiency in EF, which has been observed in children with PAE (Rasmussen, 2005), or to the more specific deficiency in arithmetic and quantitative processing that is a hallmark of FASD (e.g., Jacobson et al., 2011a). Moreover, the small sample sizes, especially of the 3 exposed groups, markedly limit the statistical power of our analysis, particularly our ability to evaluate the significance of the notable between-group differences in theta-burst patterns. Future research should attempt to replicate our findings on a larger sample, comparing mathematical and nonmathematical verification tasks and examining the pattern of both tasks as potential predictors of FASD severity. In addition, because we did not include participants with ADHD, we were not able to determine the degree to which a specific deficit in error detection is also manifest in individuals with these comorbid symptoms.

In summary, our study demonstrates that error-related theta frequency band activity during an arithmetic task is altered by PAE. This theta-burst activity differed between alcohol-exposed and nonexposed adolescents, and within the PAE group, between levels of severity of diagnosis, providing additional evidence linking PAE to deficiencies in quantitative processing. At the behavioral level, in an easy task, such as the one used here, participants can compensate for these neural deficits, to a certain extent, by relying on other neural processes, such as working or long-term memory, that depend, in part, on IQ. It is likely, however, that in more difficult tasks, compensatory processes will be less effective given that PAE-related deficits in mathematical processing continue to be evident even after statistical adjustment for IQ (Coles et al., 1991; Goldschmidt et al., 1996; Jacobson et al., 2004; Streissguth, 2008). Our finding of a specific deficit in error detection in the context of arithmetic processing has the potential to contribute to the further refinement of a neurocognitive profile for diagnosis of FASD and to inform further development of interventions, such as the Math Learning Experience (MILE) program (Kable et al., 2007), designed to help remediate specific deficits in mathematical processing commonly seen in FASD.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Alexander WH, Brown JW (2011) Medial prefrontal cortex as an action-outcome predictor. Nat Neurosci 14:1338–1344.

Avancini C, Soltész F, Szűcs D (2015) Separating stages of arithmetic verification: an ERP study with a novel paradigm. Neuropsychologia 75:322–329.

Berger A, Shmueli M, Lisson S, Ben-Shachar MS, Lindinger NM, Lewis CE, Dodge NC, Molteno CD, Meintjes EM, Jacobson JL, Jacobson SW (2019) Deficits in arithmetic error detection in infants with prenatal alcohol exposure: An ERP study. Dev Cog Neurosci 40:100722.

Burden MJ, Jacobson SW, Sokol RJ, Jacobson JL (2005) Effects of prenatal alcohol exposure on attention and working memory at 7.5 years of age. Alcohol Clin Exp Res 29:443–452.

Cohen MX (2014) Analyzing Neural Time Series Data: Theory and Practice. MIT Press, Cambridge, MA.

Cohen MX, Elger CE, Ranganath C (2007) Reward expectation modulates feedback-related negativity and EEG spectra. NeuroImage 35:968–978.

Coles CD, Brown RT, Smith IE, Platzman KA, Erickson S, Falek A (1991) Effects of prenatal alcohol exposure at school age. I. Physical and cognitive development. Neurotoxicol Teratol 13:357–367.

Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE (1997) A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. Alcohol Clin Exp Res 21:150–161.

Conejero Á, Guerra S, Abundis-Gutiérrez A, Rueda MR (2018) Frontal theta activation associated with error detection in toddlers: influence of familial socioeconomic status. Dev Sci 21:e12494.

Connor PD, Sampson PD, Bookstein FL, Barr HM, Streissguth AP (2000) Direct and indirect effects of prenatal alcohol damage on executive function. Dev Neuropsychol 18:331–354.

Croxford J, Viljoen D (1999) Alcohol consumption by pregnant women in the Western Cape. S Afr Med J 89:962–965.

Dehaene S (1992) Varieties of numerical abilities. Cognition 44:1–42.

Dehaene S, Cohen L (1995) Towards an anatomical and functional model of number processing. Math Cogn 1:83–120.

Delorme A, Makeig S (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134:9–21.

Diamond A (2013) Executive functions. Annu Rev Psychol 64:135–168.

Electrical Geodesics (2003) Net station waveform tools technical manual. s-man-200-wtfr-001. (Tech. Rep.). EGI.

Ferree TC, Luu P, Russell GS, Tucker DM (2001) Scalp electrode impedance, infection risk, and EEG data quality. Clin Neurophysiol 112:536–544.

Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN (2007) Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatrics 119:e733–e741.

Glass L, Moore EM, Akshoomoff N, Jones KL, Riley EP, Mattson SN (2017) Academic difficulties in children with prenatal alcohol exposure: presence, profile, and neural correlates. Alcohol Clin Exp Res 41:1024–1034.

Goldschmidt L, Richardson GA, Stoffer DS, Geva D, Day NL (1996) Prenatal alcohol exposure and academic achievement at age six: a nonlinear fit. Alcohol Clin Exp Res 20:763–770.

Halperin JM, Schulz KP (2006) Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. Psychol Bull 132:560–581.

Hollingshead AB (2011) Four factor index of social status. Yale J Sociol 8:21–51.

Howell KK, Lynch ME, Platzman KA, Smith GH, Coles CD (2005) Prenatal alcohol exposure and ability, academic achievement, and school functioning in adolescence: a longitudinal follow-up. J Pediatr Psychol 31:116–126.

Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, Buckley DG, Miller JH, Aragon AS, Khaole N, Viljoen DL, Jones KL, Robinson LK (2005) A practical clinical approach to diagnosis of fetal alcohol spectrum disorders : clarification of the 1996 Institute of Medicine Criteria. Pediatrics 115:39–48.

Jacobson JL, Dodge NC, Burden MJ, Klorman R, Jacobson SW (2011a) Number processing in adolescents with prenatal alcohol exposure and ADHD: differences in the neurobehavioral phenotype. Alcohol Clin Exp Res 35:431–442.

Jacobson SW, Chiodo LM, Sokol RJ, Jacobson JL (2002) Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome. Pediatrics 109:815–825.

Jacobson SW, Jacobson JL, Sokol RJ, Chiodo LM, Corobana R (2004) Maternal age, alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. Alcohol Clin Exp Res 28:1732–1745.

Jacobson SW, Jacobson JL, Sokol RJ, Martier SS, Ager JW (1993) Prenatal alcohol exposure and infant information processing ability. Child Dev 64:1706–1721.

Jacobson SW, Jacobson JL, Stanton ME, Meintjes EM, Molteno CD (2011b) Biobehavioral markers of adverse effect in fetal alcohol spectrum disorders. Neuropsychol Rev 21:148–166.

Jacobson SW, Stanton ME, Molteno CD, Burden MJ, Fuller DS, Hoyme HE, Robinson LK, Khaole N, Jacobson JL (2008) Impaired eyeblink conditioning in children with fetal alcohol syndrome. Alcohol Clin Exp Res 32:365–372.

Kable JA, Coles CD, Taddeo E (2007) Socio-cognitive habilitation using the math interactive learning experience program for alcohol-affected children. Alcohol Clin Exp Res 31:1425–1434.

Kaufmann L, Koppelstaetter F, Delazer M, Siedentopf C, Rhomberg P, Golaszewski S, Felber S, Ischebeck A (2005) Neural correlates of distance and congruity effects in a numerical Stroop task: an event-related fMRI study. NeuroImage 25:888–898.

Kerns KA, Don A, Mateer CA, Streissguth AP (1997) Cognitive deficits in nonretarded adults with fetal alcohol syndrome. J Learn Disabil 30:685–693.

Kopera-Frye K, Dehaene S, Streissguth AP (1996) Impairments of number processing induced by prenatal alcohol exposure. Neuropsychologia 34:1187–1196.

Lenth R (2018) emmeans: Estimated Marginal Means, aka Least-Squares Mean. It is a statistical software.

Lewis CE, Thomas KG, Dodge NC, Molteno CD, Meintjes EM, Jacobson JL, Jacobson SW (2015) Verbal learning and memory impairment in children with fetal alcohol spectrum disorders. Alcohol Clin Exp Res 39:724–732.

Luck SJ (2014) An Introduction to the Event-Related Potential Technique. MIT Press, Cambridge, MA.

Luu P, Tucker DM, Derryberry D, Reed M, Poulsen C (2003) Electrophysiological responses to errors and feedback in the process of action regulation. Psychol Sci 14:47–53.

Mattson SN, Roebuck TM (2002) Acquisition and retention of verbal and nonverbal information in children with heavy prenatal alcohol exposure. Alcohol Clin Exp Res 26:875–882.

May PA, Blankenship J, Marais A-S, Gossage JP, Kalberg WO, Barnard R, De Vries M, Robinson LK, Adnams CM, Buckley D (2013) Approaching the prevalence of the full spectrum of fetal alcohol spectrum disorders in a South African population-based study. Alcohol Clin Exp Res 37:818–830.

Meintjes EM, Jacobson JL, Molteno CD, Gatenby JC, Warton C, Cannistraci CJ, Hoyme HE, Robinson LK, Khaole N, Gore JC (2010) An FMRI study of number processing in children with fetal alcohol syndrome. Alcohol Clin Exp Res 34:1450–1464.

Menon V, Rivera SM, White CD, Glover GH, Reiss AL (2000) Dissociating prefrontal and parietal cortex activation during arithmetic processing. NeuroImage 12:357–365.

R Core Team (2018) R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

Rasmussen C (2005) Executive functioning and working memory in fetal alcohol spectrum disorder. Alcohol Clin Exp Res 29:1359–1367.

Santhanam P, Li Z, Hu X, Lynch ME, Coles CD (2009) Effects of prenatal alcohol exposure on brain activation during an arithmetic task: an fMRI study. Alcohol Clin Exp Res 33:1901–1908.

Shenhav A, Botvinick MM, Cohen JD (2013) The expected value of control: an integrative theory of anterior cingulate cortex function. Neuron 79:217–240.

Singmann H, Bolker B, Westfall J, Aust F (2018) afex: Analysis of Factorial Experiments.

Sowell ER, Mattson SN, Kan E, Thompson PM, Riley EP, Toga AW (2008) Abnormal cortical thickness and brain-behavior correlation patterns in individuals with heavy prenatal alcohol exposure. Cereb Cortex 18:136–144.

Streissguth AP (1994) A long-term perspective of FAS. Alcohol Health Res World 18:74–74.

Streissguth AP, Barr HM, Sampson PD (1990) Moderate prenatal alcohol exposure: effects on child IQ and learning problems at age 7 1/2 years. Alcohol Clin Exp Res 14:662–669.

Tucker DM (1993) Spatial sampling of head electrical fields: the geodesic sensor net. Electroencephalogr Clin Neurophysiol 87:154–163.

Tzur G, Berger A (2007) When things look wrong: theta activity in rule violation. Neuropsychologia 45:3122–3126.

Tzur G, Berger A (2009) Fast and slow brain rhythms in rule/expectation violation tasks: focusing on evaluation processes by excluding motor action. Behav Brain Res 198:420–428.

Tzur G, Berger A, Luria R, Posner MI (2010) Theta synchrony supports Weber-Fechner and Stevens' Laws for error processing, uniting high and low mental processes. Psychophysiology 47:758–66.

Vaurio L, Riley EP, Mattson SN (2008) Differences in executive functioning in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. J Int Neuropsychol Soc 14:119–129.

Woods KJ, Jacobson SW, Molteno CD, Jacobson JL, Meintjes EM (2018) Altered parietal activation during non-symbolic number comparison in children with prenatal alcohol exposure. Front Hum Neurosci 11: 627.

Woods KJ, Meintjes EM, Molteno CD, Jacobson SW, Jacobson JL (2015) Parietal dysfunction during number processing in children with fetal alcohol spectrum disorders. NeuroImage Clin 8:594–605.