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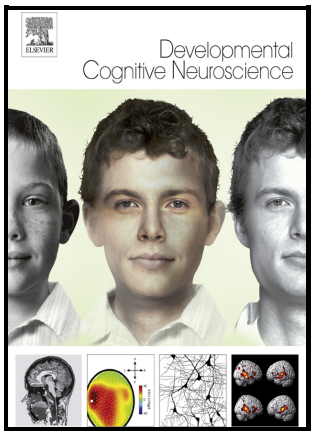

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Decreased resting-state alpha peak frequency in children and adolescents with fetal alcohol spectrum disorders or prenatal alcohol exposure

Felicha T. Candelaria-Cook[1*], Megan E. Schendel[1], Lucinda Flynn[1], Cassandra Cerros[2], Piyadasa Kodituwakku[3], Ludmila N. Bakhireva[4], Dina E. Hill[2], Julia M. Stephen[1]

[1]The Mind Research Network and Lovelace Biomedical Research Institute, Albuquerque, New Mexico, USA.

[2]Psychiatry, University of New Mexico, Albuquerque, NM.

[3]Pediatrics, University of New Mexico, Albuquerque, NM.

[4]Substance Use Research and Education Center, College of Pharmacy, University of New Mexico, Albuquerque, NM.

*** Corresponding Author:**

Felicha Candelaria-Cook, PhD

The Mind Research Network

1101 Yale Blvd NE

Albuquerque, NM 87106

Email: fccook@mrn.org

Phone: (505) 272-5028

Fax: (505) 272-8002

Abstract

Prenatal alcohol exposure (PAE) can result in long-lasting changes to physical, behavioral, and cognitive functioning in children. PAE might result in decreased white matter integrity, corticothalamic tract integrity, and alpha cortical oscillations. Previous investigations of alpha oscillations in PAE/fetal alcohol spectrum disorder (FASD) have focused on average spectral power at specific ages; therefore, little is known about alpha peak frequency (APF) or its developmental trajectory making this research novel. Using resting-state MEG data, APF was determined from parietal/occipital regions in participants with PAE/FASD or typically developing controls (TDC). In total, MEG data from 157 infants, children, and adolescents ranging in age from 6 months to 17 years were used, including 17 individuals with PAE, 61 individuals with an FASD and 84 TDC. In line with our hypothesis, we found that individuals with PAE/FASD had significantly reduced APF relative to TDC. Both age and group were significantly related to APF with differences between TDC and PAE/FASD persisting throughout development. We did not find evidence that sex or socioeconomic status had additional impact on APF. Reduced APF in individuals with an FASD/PAE may represent a long-term deficit and demonstrates the detrimental impact prenatal alcohol exposure can have on neurophysiological processes.

Keywords:

Fetal Alcohol Spectrum Disorder$_1$, MEG$_2$, resting-state$_3$, PAE$_4$, Peak Alpha$_5$.

1 Introduction

Alcohol use in pregnancy remains highly prevalent with recent estimates ranging from 13.5% (Gosdin et al., 2022) to 30.3% (Ethen et al., 2009). Alcohol consumption in early pregnancy, including binge drinking, has been estimated to be as high as 24.4% in the general obstetrics population (Bakhireva et al., 2018). Prenatal alcohol exposure (PAE) can result in detrimental changes to physical, behavioral, and cognitive functioning in children that persist throughout the lifetime. Fetal alcohol spectrum disorders (FASD), an umbrella term for disorders due to PAE, include children with fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol-related neurodevelopmental disorder (ARND), and neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE). Current prevalence of FASD in the US based on active case ascertainment was estimated to be between 1-5% of school-aged children (May et al., 2018), with some estimates of FASD prevalence up to 8.3% in the rocky mountain region (May et al., 2020) and 7.1% in the southeastern region (May et al., 2021). Recent research also estimates less than 1% of children who meet the criteria for an FASD will be diagnosed (Popova et al., 2020). Data based on parental reports from the large nationwide Adolescent Brain Cognitive Development study indicate 25.9% of adolescent participants had been exposed to alcohol in utero (Briana Lees et al., 2020). When combined, these population statistics indicate there are high rates of both diagnosed and undiagnosed cases of FASD in the US, with many children with PAE without early identifiable markers. This indicates a high need for understanding the neurophysiological impact of PAE on the developing brain.

Structurally, children with FASD have widespread decreases in white matter integrity (Lebel et al., 2008, Sowell et al., 2008), decreased corpus callosum thickness (Riley et al., 1995), microstructural abnormalities (Honey et al., 2012), and reduced fractional anisotropy (FA) in white matter tracts (Wozniak et al., 2006, Lebel et al., 2008, Sowell et al., 2008, Paolozza et al., 2017), including corticothalamic tracts (Stephen et al., 2021). Functionally, the structural differences reported in children with FASD have resulted in impaired cortico-cortical connections during a resting-state. For example, studies have reported impaired interhemispheric and white matter connectivity (Wozniak et al., 2013), along with reduced default network functional connectivity (Wozniak et al., 2011, Santhanam et al., 2011, Wozniak et al., 2017).

At the neurophysiological level, children with an FASD have been reported to have abnormal neural oscillations during a resting-state. In infancy, 6-month-olds with PAE have higher spectral power across all frequency bands (1-58 Hz) when compared to typically developing infants (Havlicek et al., 1977, Chernick et al., 1983, Ioffe et al., 1984, Stephen et al., 2018). Conversely, by 8-12 years of age, alpha oscillations are reduced in children with FAS within superior parietal and lateral occipital cortex (Candelaria-Cook et al., 2021). Cortical alpha power is directly influenced by integrity of corticothalamic tracts (Hughes and Crunelli, 2005, Hughes et al., 2011) in typically developing children but not in children with FASD (Stephen et al., 2021), indicating the need to examine other neural oscillation variables, such as alpha peak frequency. However, to date, no studies have explored alpha peak frequency following PAE. Other evidence of altered local dynamics is the increased entropy in the right hemisphere of children with FAS (Candelaria-Cook et al., 2021). In task-based studies, adolescents with an FASD have shown decreased gamma oscillatory power (Stephen et al., 2013, Bolanos et al., 2017), along with greater beta oscillatory power (Bolanos et al., 2017).

The alpha peak frequency, or the frequency with the largest amplitude alpha activity within the 8-12 Hz range in adults, usually increases gradually as a function of age throughout childhood and adolescence in typically developing children (Cragg et al., 2011, Somsen et al., 1997, Miskovic et al., 2015, Edgar et al., 2019). To account for this age-related change, studies in infants define the alpha range for 6-month-old infants to occur in the 6-9 Hz range. In certain developmental disorders, such as autism spectrum disorder (ASD), there have been instances of abnormal maturation of alpha peak frequency (Dickinson et al., 2018, Green et al., 2022, Edgar et al., 2019) accompanying either increased alpha power (Edgar et al., 2015, Cornew et al., 2012) or decreased alpha power (Chan et al., 2007, Sheikhani et al., 2012). Specifically, in children with ASD, alpha peak frequency does not increase as a function of age (Dickinson et al., 2018, Edgar et al., 2019) as it does in typically developing controls (TDC). Cortico-thalamic tracts and white matter architecture may be responsible for generating resting alpha oscillations (Valdés-Hernández et al., 2010), along with thalamic pacemaker neurons. In TDC, right thalamic volume and alpha peak frequency were positively correlated, a relationship which was not present in children with ASD, yet the group difference was not significant (Green et al., 2022). Alpha peak frequency may be abnormal in developmental disorders especially when cortical-thalamic tracts are compromised and volumetric or spectral differences are also present.

The current study was designed to assess alpha peak frequency in children with PAE/FASD and TDC by examining associations between brain structure and alpha peak frequency. Previous examinations of alpha oscillations in PAE/FASD have focused on group differences in average spectral power (Stephen et al., 2018, Candelaria-Cook et al., 2021); therefore, this is one of the first neurophysiological studies examining alpha peak frequency in PAE/FASD. Based on previous spectral power findings (Candelaria-Cook et al., 2021), we hypothesized that children with PAE/FASD would have reduced alpha peak frequency relative to healthy controls. We also hypothesize that their alpha peak frequency may vary with age consistent with younger children with PAE showing slight elevation in alpha power (Stephen et al., 2018) and older children with FASD showing reduced alpha power (Candelaria-Cook et al., 2021). Here, we focus on alpha peak frequency within the parietal/occipital cortex, given that alpha oscillations during a resting-state typically peak in these regions (Edgar et al., 2019, Hari and Salmelin, 1997, Haegens et al., 2014). Using data from multiple cross-sectional studies, the alpha peak frequency in the eyes-open resting-state was determined from parietal and occipital sensor regions for 157 infants, children, and adolescents (age range 6 months-17 years) with PAE/FASD or TDC.

2 Materials and Methods

2.1 Participants

For the present study, data were pooled from 5 separate studies conducted at the Mind Research Network and University of New Mexico Health Sciences Center (UNM-HSC) in Albuquerque, New Mexico (Stephen et al., 2012, Stephen et al., 2013, Candelaria-Cook et al., 2021, Stephen et al., 2021, Stephen et al., 2018). In total, 157 infants, children and adolescents (4 months-17 years of age) were included: 17 with PAE, 61 with an FASD, and 84 TDC. Infants (n=23, TDC=12/PAE=11) were recruited as a part of the ENRICH-1 study and their mothers were identified during pregnancy from prenatal care clinics at the University of New Mexico (Stephen et al., 2018, Bakhireva et al., 2015). A subset of PAE and TDC infants enrolled in the ENRICH-1 study who completed 6-month MEG evaluations were included here. To be included infants needed high quality MEG data with a distinguishable, single alpha peak, visual within the 6-13 Hz range. PAE in infants was determined by maternal self-report (timeline follow-back interviews) during pregnancy or positive biomarker(s) for alcohol metabolites. The screening panel included gamma-

glutamyltranspeptidase, carbohydrate-deficient transferrin, phosphatidylethanol, urine ethyl sulfate, and urine ethyl glucurodine in mothers and PEth (PEth-DBS) from a dry blood spot in newborns (Bakhireva et al., 2015). The remaining participants with an FASD (n=61) or PAE (n=6) were recruited from the Prenatal Exposures Clinic within the Center for Development and Disability at the UNM-HSC. Participants were classified as having a prenatal alcohol exposure-related diagnosis including FAS, pFAS, or ARND using diagnostic criteria by (Hoyme et al., 2016, Stratton et al., 1996). FASD classification was based on consensus and assessment from an interdisciplinary team with a clinical psychologist, neuropsychologist, and pediatrician. Maternal alcohol consumption was confirmed either through direct confirmation by maternal interview, eyewitness reports of maternal drinking during pregnancy, or legal records confirming alcohol consumption during pregnancy (e.g. DWI arrest). Information on maternal alcohol consumption during pregnancy is collected as a part of the FASD clinical assessment; however, accurate estimates of quantity of alcohol consumption during pregnancy are often not available. For the current study the combined group of PAE/FASD reflects infants and younger children with known PAE, along with children and adolescents with a diagnosed FASD. While children with dysmorphology associated with FAS can be diagnosed as early as 8 months of age, with the average FAS diagnosis age at 48.3 months or 4 years (Moberg et al., 2014), the average age of diagnosis for the broader FASD spectrum, which make up the vast majority of FASD cases and are difficult to diagnose, is 5.7 years (Palmeter et al., 2021) to 9 years; therefore, younger children in the study without a diagnosis but with confirmed prenatal alcohol exposure are referred to as PAE. TDC did not have known prenatal exposure to alcohol or other substances; nor did they have histories of developmental delays or neurological or psychological problems. Research protocols were approved by the University of New Mexico Health Sciences Center Human Research Review Committee (UNM HSC HRRC) and were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments on ethical standards. Informed consent/assent was obtained from all participants and their parents.

The 5 separate studies from which data are pooled are referred to as S1-S5 in Table 1, further information on each study is provided within references, S1 (Stephen et al., 2021, Candelaria-Cook et al., 2021), S2 (ongoing study not yet published), S3 (Coffman et al., 2020, Bolanos et al., 2017, Stephen et al., 2013), S4 (Stephen et al., 2012), S5 (Stephen et al., 2018). Each study (S1-S5) had unique aims and protocols, but were similar in that they were conducted in FASD/PAE populations and included resting-state data. While the recruitment age of each study varied, each study collected 2-5 minutes of eyes-open resting state data with similar resting-state paradigms at the same data collection site (MRN). Briefly the aims of the studies were related to the following: attention (S1 & S2) and multisensory and unisensory responses (S3, S4, & S5).

Table 1: Participant Characteristics

	TDC (Mean ±SEM)	**PAE/FASD** (Mean ±SEM)
Demographics		
Gender (M/F)	43/41	37/36
Male average age (years)	8.44 ±0.72	9.84 ±0.71
Male age range	0.60-17.92	0.43-17.92
Female average age (years)	8.61 ±0.71	8.17 ±0.79
Female age range	0.50-17.66	0.50-17.17
Barrett SES*	44.49 ±1.91	33.60 ±2.30
Barrett SES range	16.00-65.50	11.50-66.00
S1 average age (years)	10.74 ±0.37	10.87 ±0.40
S1 sample size (total n)	31	27
S1 Gender (M/F)	14/17	10/17
S2 average age (years)	7.31 ±0.24	7.62 ±0.19
S2 sample size (total n)	17	13
S2 Gender (M/F)	8/9	10/3
S3 average age (years)	15.21 ±0.62	14.52 ±0.54
S3 sample size (total n)	12	14
S3 Gender (M/F)	6/6	9/5
S4 average age (years)	5.61 ±0.37	6.23 ±0.51
S4 sample size (total n)	12	9
S4 Gender (M/F)	9/3	5/4
S5 average age (years)	0.73 ±0.03	0.62 ±0.04
S5 sample size (total n)	12	10
S5 Gender (M/F)	6/6	3/7
Data Quality	(Mean ±SD)	(Mean ±SD)
Total # of eyes open epochs	66.40 ±6.65	65.36 ±6.52
Total % epochs rejected	6.02 ±1.54	7.53 ±1.81
S1 # of eyes open epochs	29.65 ±0.78	29.93 ±0.35
S1 % epochs rejected	4.37 ±2.53	3.46 ±1.13
S2 # of eyes open epochs	133.59 ±13.82	117.46 ±14.29
S2 % epochs rejected	9.55 ±5.14	18.16 ±8.56
S3 # of eyes open epochs	152.50 ±3.50	140.43 ±7.69
S3 % epochs rejected	0.86 ±0.46	1.06 ±0.29
S4 # of eyes open epochs	30.08 ±0.83	30.22 ±0.36
S4 % epochs rejected	2.96 ±2.68	2.51 ±1.18
S5 # of eyes open epochs	16.17 ±2.97	19.80 ±3.12
S5 % epochs rejected	13.50 ±2.73	18.30 ±3.20

2.2 MRI Data Acquisition

Structural MRIs were obtained from 67% of participants of the total sample. Select studies, S1-S3, collected structural MRIs used here. Sagittal T1-weighted anatomical MR images were obtained using a 3T Siemens Triotim MRI system with a 32-channel head coil or a 3T Siemens Prisma MRI system with a 32-channel head coil. The parameters of the multiecho 3D MPRAGE sequence on the Siemens Triotim were as follows: TR/TE/TI = 2530/1.64, 3.5, 5.36, 7.22, 9.08/1200 ms, flip angle = 7°, field of view (FOV) = 256 mm x 256 mm, matrix = 256 x 256, 1 mm thick slice, 192 slices, GRAPPA acceleration factor = 2. The parameters of the MPRAGE sequence on the Siemens Prisma were as follows: TR = 2500 ms, TE= 2.88 ms, TI= 1060 ms, flip angle = 8°, field of view (FOV) = 256 mm x 256 mm, matrix = 256 x 256, resolution=1.0 x 1.0 x 1.0 mm, 176 slices, parallel imaging = 2x.

Cortical reconstruction and volumetric segmentation were performed with Freesurfer 5.3 software; details on the method can be found at (http://surfer.nmr.mgh.harvard.edu/) and (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferMethodsCitation). From each subject's structural MPRAGE scan, tissue was automatically segmented into gray and white matter and summarized in an aseg atlas morphometry table of volume and intensity statistics. We examined the following values: cortical white matter volume, subcortical gray matter volume (volume of structures including thalamus, caudate, putamen, pallidum, hippocampus, amygdala, accumbens, and substantia nigra), total gray matter volume (sum of cortex, subcortical gray and cerebellum gray), and left and right thalamus volume. The estimated total intracranial volume measure was used as a covariate when necessary to account for brain volume differences.

2.3 MEG Data Acquisition

All MEG data were collected at the Mind Research Network in a magnetically shielded room using a whole-cortex 306-channel MEG system (Elekta MEGIN). Prior to data acquisition, two electroculogram electrodes were placed near the left and right eye to capture eye movements for artifact removal in children and adolescents, but not infants. Two electrocardiogram electrodes were placed below the left and right clavicles to capture heartbeat for artifact removal in all participants. Three-dimensional digitization equipment (Polhemus FastTrack) was used to register the location of four head position indicator (HPI) coils located on the mastoid bone and upper forehead. The HPI coils allow for measurement of the head position within the MEG helmet during data collection. Using the digitization equipment, the head coordinate system was defined by the left and right preauricular and nasion fiducial points, along with general head shape. During the scan, children and adolescents sat upright in the scanner and were monitored by audio and video links in the control room. All infants were measured in supine position with the left hemisphere positioned close to the dewar and were accompanied in the scanning room by a parent/guardian and study researcher. Infant sessions were recorded on video for later behavioral analysis (Stephen et al., 2018). Data were sampled at 1 kHz with an acquisition passband of 0.1–330 Hz. Continuous HPI monitoring (cHPI) was enabled to allow for movement correction.

Eyes-open resting-state data were pooled from separate studies and protocols. Children and adolescent participants were instructed to rest quietly while a white fixation cross was present on the center of the screen (Candelaria-Cook et al., 2021) or visual stimuli played without sound (Coffman et al., 2020). In infants, rest and play periods with the investigator and parents were coded with video-recording and physiological monitoring channels to identity behavior during data collection (Stephen et al., 2018). The duration of the resting-state task ranged from 1 to 5 minutes in an eyes-open state depending on study. For all studies, for data to be included here, there needed to be a distinguishable, single alpha peak, visual within the 6-13 Hz range within high quality MEG data. In each study the number of datasets screened and included was as follows: S1 (58/58), S2 (30/30),

S3 (32/33), S4 (21/21), S5 (22/78).

2.4 MEG Data Processing

Raw MEG data were processed with Neuromag Max-Filter 2.1 and 2.2 software using the temporal extension of signal space separation (t-SSS) with movement compensation (Taulu and Kajola, 2005, Taulu and Hari, 2009). Sensor space data were transformed to an average head position across subjects relative to the helmet array using Maxfilter 2.1 and 2.2 MaxMove option. Each individual study had its own average head position maximized for age range. This procedure transforms the MEG data such that each sensor is in an equivalent location relative to the head coordinate system across subjects. Using MNE software (Gramfort et al., 2013), signal space projection (SSP) (Uusitalo and Ilmoniemi, 1997) was used to remove heartbeat and eye-blink artifacts for children and adolescent data. Data from 6-month-old infants in the ENRICH-1 study were processed as described in (Stephen et al., 2018). For infant data, heartbeat signal was removed using Graph due to the fact that multiple projectors are needed to remove heartbeat artifact from infant data (Uusitalo and Ilmoniemi, 1997). Furthermore, visual inspection in combination with session information was used to identify 2 second intervals of noise-free MEG activity (Stephen et al., 2018). Rejection thresholds were set to 6 picotesla for magnetometers and 4 picotescla for gradiometers. All spectral data were exported to MATLAB (2018a, MathWorks) and further analyzed via custom scripts.

To accommodate the ongoing development of alpha oscillations from infancy to adulthood the alpha frequency band was defined as 6-13 Hz. To calculate alpha peak, time courses from 64 planar gradiometers in the parietal and occipital regions were extracted. Spectral power from 16 sensor pairs or 32 individual gradiometers from parietal region and 16 sensor pairs or 32 individual gradiometers from occipital region were extracted, see Figure 1. Alpha peak frequency was defined as the maximum alpha peak frequency within the 6-13 Hz range. Power spectra were examined visually, in combination with a custom MATLAB script, to determine the frequency at which alpha power was maximal in the posterior channel. The maximum peak from all 64 sensors was confirmed with visual inspection.

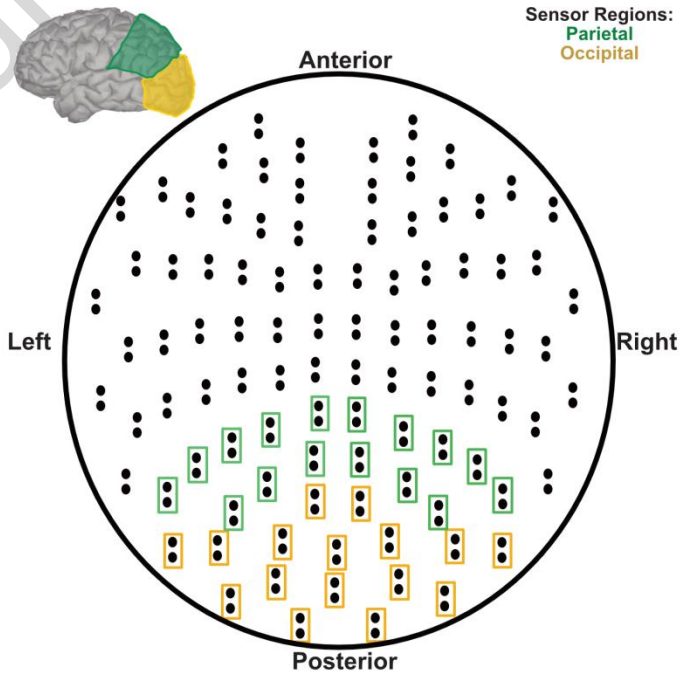

Figure 1: Alpha peak Sensor Channels. Spectral power was extracted from 32 parietal and 32 occipital planar gradiometers. Alpha peak frequency was defined as the maximum alpha peak frequency within the 6-13 Hz range from 64 gradiometers in the parietal or occipital regions.

2.5 Statistical Analysis

Statistics were performed using SPSS, version 28 for Macintosh (IBM). Univariate analysis of variance (ANOVA) was used to evaluate group differences in participant demographics and data quality with the statistical threshold set at $p<0.05$. For the ANOVA, group (TDC, PAE/FASD) was the between subject factor. Barrett SES was not available for the entire sample and those with missing values were dropped from the specific analysis. Univariate analysis of covariance (ANCOVA) was used to evaluate group differences in alpha peak power with the statistical threshold set at $p<0.05$. For the ANCOVA, group (TDC, PAE/FASD) and sex (female, male) were the between subject factors and age was the covariate. Hierarchical regressions were used to evaluate alpha peak frequency and age. For the hierarchical regression, age was entered first, group was entered second, and the interaction term was entered last. Interactions between age and group were tested to determine if different developmental trajectories exist, i.e. whether differences between groups are present at younger or older ages or whether the group differences persist throughout development. The age and group interaction evaluated different linear trends between group. Partial correlations controlling for total brain volume were used to examine relationships between alpha peak frequency and structural MRI brain volume. Graphed data from partial correlations are standardized residuals after removing variation from total brain volume. To test for group differences in alpha peak frequency and structural MRI brain volume correlation values a Fisher's r-to-z transformation was done. To control for type 1 error, false discovery rate (FDR) correction was used to correct for multiple comparisons.

3 Results

3.1 Participants and Data Quality

Sample demographic information is presented in Table 1, asterisks represent significant group differences. Group differences in average age, gender, and Barrett SES were examined. The sample was well matched in terms of male and female average age, and gender, $p>0.05$. Individual statistics are not reported as all ANOVA group comparisons are $p>0.05$. For the Barrett SES measure, the PAE/FASD group had significantly lower SES when compared to TDC, $F(1,88)=13.503$, $p<0.001$.

Data quality was assessed by verifying that TDC and individuals with PAE/FASD had equivalent MEG epoch numbers and percent epochs rejected. There were no main effects of group or group differences in the number of eyes open epochs processed or percent of epochs rejected in any of the 5 individual studies included (S1-S5), as shown in Table 1, *p* values >0.189. TDC and PAE/FASD had equivalent MEG epoch numbers and percent epochs rejected overall and in each individual study. Individual statistics are not reported as all ANOVA group comparisons are $p>0.05$.

3.2 Alpha Peak Frequency Group Difference

Group differences in alpha peak were investigated with ANCOVA with age as the covariate. Individuals with PAE/FASD had significantly lower alpha peak frequency (APF) than typically developing controls, APF_{FASD}= 9.171 Hz compared to APF_{TDC}= 9.585 Hz (Group $F(1,154)=6.081$,

p=0.015), see Figure 2. The covariate, age, was significantly related to alpha peak frequency, F(1,154)=24.219, p=<0.001, r=0.37, and indicates alpha peak frequency increases with age.

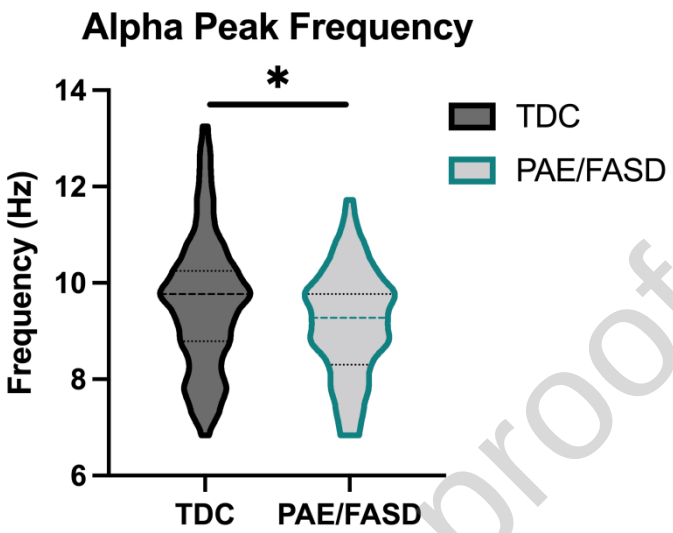

Figure 2: Alpha Peak Frequency Group Difference. Participants with PAE/FASD had significantly reduced alpha peak frequency when controlling for age, p=0.015.

Analyses also explored the impact of sex on alpha peak frequency, as previous studies have indicated males and females may have different alpha peak frequencies and alpha maturation rates. We found no impact of sex on alpha peak frequency in TDC (APF_F= 9.671 Hz compared to APF_M= 9.504 Hz) or in PAE/FASD (APF_F= 9.265 Hz compared to APF_M= 9.080 Hz) and no interaction between sex and group, all p's>0.179. There were no significant age differences between males and females in either group, p>0.120, see table 1. Given the lack of differences in alpha peak frequency between males and females, subsequent analyses did not include sex in models.

3.3 Alpha Peak Group Differences Across Age

A three-stage hierarchical multiple regression was used to examine variables predicting alpha peak frequency. In the first stage, age was entered to control for development. Group was entered at stage two, and an interaction between age by group was entered at the third stage. Multiple regression variables are reported in Table 2. The hierarchical multiple regression revealed age and group significantly predicted alpha peak frequency, but there was no interaction between age and group, p=0.088. There was a positive relationship between age and alpha peak frequency (r=0.364, p<0.001) indicating alpha peak frequency increased as age increased, Figure 3. The group difference indicates TDC and PAE/FASD have significantly different alpha peak frequencies. The lack of an interaction between age and group indicate group differences persist throughout development. We also examined group differences in alpha peak across age with infant data (S5) removed; however, the main results were similar with and without infant data. Without the infant data, the hierarchical multiple regression revealed age, p<0.001, and group, p=0.003, significantly predicted alpha peak frequency, but there was no interaction between age and group, p=0.308.

Table 2: Summary of Hierarchical Regression Analysis for Variables Predicting Alpha Peak Frequency

Variable	B	SE B	beta	*t*	*p*-value
Step 1					
Constant	8.532 (8.114, 8.904)	0.206	.354	41.480	<0.001
Age	0.098 (0.057, 0.144)	0.021		4.719	
Step 2					
Constant	8.724 (8.247, 9.116)	0.217		40.234	
Age	0.101 (0.063,0.147)	0.021	.364	4.921	<0.001
Group	-0.464 (-0.820,-0.124)	0.188	-.183	-2.466	0.015
Step 3					
Constant	8.447 (7.874, 8.955)	0.269		31.391	
Age	0.134 (0.075, 0.199)	0.028	.481	4.801	<0.001
Group	0.154 (-0.651, 0.945)	0.405	.061	0.381	0.704
Interaction	-0.070 (-0.155, 0.013)	0.041	-.303	-1.719	0.088

Model values:
R^2=0.126 for Step 1; change R^2=0.033 for Step 2; change R^2=0.016 for Step 3

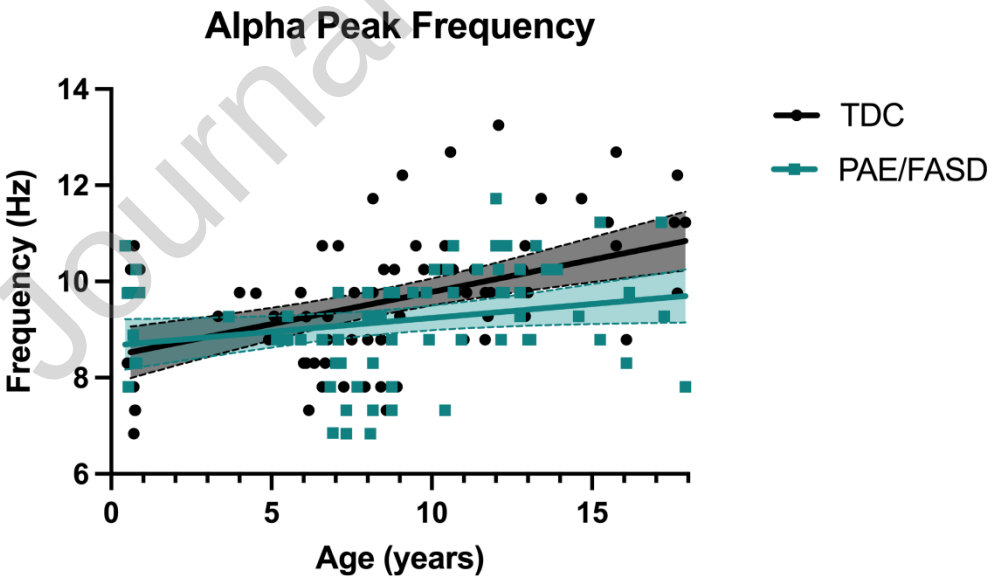

Figure 3: Alpha Peak Frequency by Age. Age and group significantly predicted alpha peak frequency. In both groups, alpha peak frequency increased as age increased. Group differences indicate differences between TDC and PAE/FASD persist throughout development

3.4 Alpha Peak Frequency and Brain Structure

The relationship of alpha peak frequency and brain structure was investigated in a subset of participants (TDC=53, PAE/FASD=49) who had MRIs, those from S1-S3 with age range from 6-17.92 years of age. Data from 3 TDC outliers were removed. Correlations with cerebral white matter volume, subcortical gray matter volume, total gray matter volume, left thalamus volume and right thalamus volume were examined. Partial correlations using FreeSurfer's total brain volume measure (estimated total intracranial volume) were used to account for variation in head size. Data shown in Figure 4 are standardized residuals after removing variation from total brain volume. In the overall sample, after multiple comparisons correction, there was a significant positive correlation between higher alpha peak frequencies and more cerebral white matter volume [r=0.244, 95% BCA CI [0.045,0.413], R^2=0.06, p=0.014], and a negative correlation between higher alpha peak frequencies and less total gray matter volume [r=-0.418, 95% BCA CI [-0.579,-0.242], R^2=0.17, p<0.001], Figure 4. The relationship between alpha peak frequency and brain structure was also investigated within each group. After correction for multiple comparisons among brain structures, within TDC there was a significant positive correlation between higher alpha peak frequencies and more cerebral white matter volume [r=0.375, 95% BCA CI [0.134,0.608], R^2=0.14, p=0.006] but not within PAE/FASD [r=0.109, 95% BCA CI [-0.238,0.373], R^2=0.01, p=0.461]; this group difference was not significant (z=1.39, p=0.08), Figure 4. Within TDC, there was a significant negative correlation between higher alpha peak frequencies and less total gray matter volume [r=-0.423, 95% BCA CI [-0.687,-0.113], R^2=0.18, p=0.002] and within PAE/FASD, there was a significant negative correlation between higher alpha peak frequencies and less total gray matter volume [r=-0.496, 95% BCA CI [-0.706,-0.220], R^2=0.25, p<0.001]; this group difference was not significant (z=0.45, p=0.32), Figure 4. Although the following comparisons did not survive multiple comparison corrections among brain structures, a couple interesting trends that are worth mentioning include relationships within thalamus: a positive correlation between higher alpha peak frequencies and larger right thalamus volume in TDC [r=0.267, 95% BCA CI [-0.021,0.528], R^2=0.07, p=0.05], but not PAE/FASD [r=-0.173, 95% BCA CI [-0.442,0.100], R^2=0.03, p=0.240], group difference (z=2.19, p=0.014), and a negative correlation between higher alpha peak frequencies and less left thalamus volume in PAE/FASD [r=-0.305, 95% BCA CI [-0.540,-0.072], R^2=0.09, p=0.035], but not TDC [r=0.102, 95% BCA CI [-0.171,0.385], R^2=0.01, p=0.472], group difference (z=2.04, p=0.021), Figure 4.

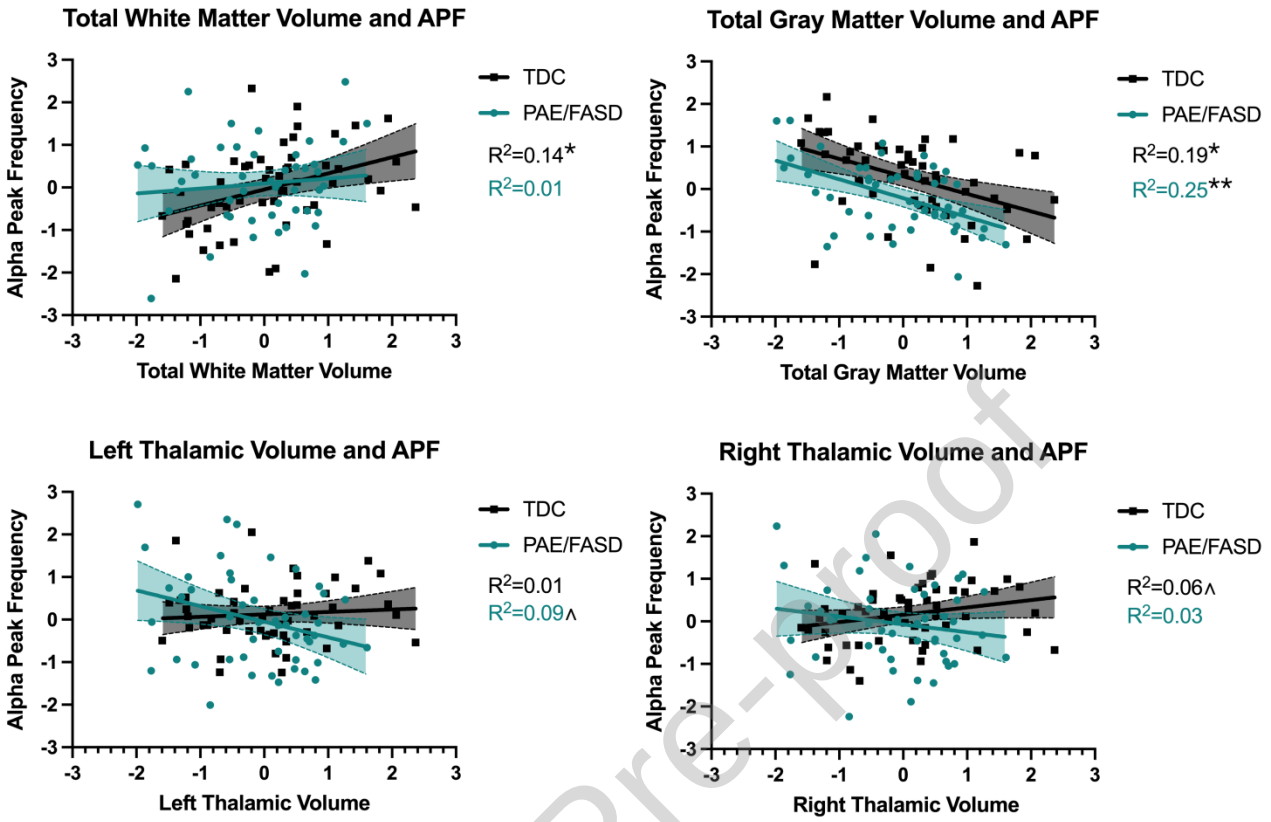

Figure 4: Alpha Peak Frequency and Brain Structure. Scatterplots showing associations between alpha peak frequency and total white matter volume (top left), total gray matter volume (top right), left thalamic volume (bottom left), and right thalamic volume (bottom right). Data shown are standardized residuals after removing variation from total brain volume. Top Left: Positive correlation between higher alpha peak frequencies and more total white matter volume in TDC but not PAE/FASD. Top Right: Negative correlation between higher alpha peak frequencies and less total gray matter volume in TDC and PAE/FASD. Bottom Left: Negative correlation between higher alpha peak frequencies and less left thalamic volumes in PAE/FASD but not TDC. Bottom Right: Positive correlation between higher alpha peak frequencies and larger thalamic volumes in TDC but not PAE/FASD. *p<0.05;**p<0.001;^p<0.05 prior to multiple comparisons correction.

3.5 Alpha Peak Frequency and SES

The relationship of alpha peak frequency and SES was investigated in a subset of participants (TDC=48, PAE/FASD=42) for which SES was available, those from S1, S2, and S5 with an age range from 6 months-16.08 years of age. In the overall sample there was a trend approaching significance with higher alpha peak frequencies associated with higher SES levels [r=0.182, 95% BCA CI [-0.013, 0.349], R^2=0.03, p=0.086]. When the correlation between alpha peak frequency and SES was explored within each group, there was no association of alpha peak frequency with SES, [TDC r=0.196, R^2=0.04, p=0.182][PAE/FASD r=0.140, R^2=0.02, p=0.378], group difference (z=0.26, p=0.397].

4 Discussion

As we hypothesized, based on previous spectral power findings (Stephen et al., 2018, Candelaria-Cook et al., 2021), individuals with an FASD or PAE had reduced alpha peak frequency relative to TDC. Also, as expected, age was significantly related to alpha peak frequency, with alpha peak frequency increasing with age in both groups. Also, group effects were present which indicate differences between TDC and PAE/FASD persist throughout development. While the interaction term between age and group was not significant, there was a trend for maturation rates not being equal between TDC and PAE/FASD and group differences becoming more apparent in adolescence. We also found a positive correlation between alpha peak frequency and total cerebral white matter volume in the total sample, and in TDC, with correlation values being significantly different between groups. Within PAE/FASD there was a significant negative correlation between higher alpha peak frequencies and less total gray matter volume, but not in TDC, although the group difference was not significant. Interestingly, we also found group specific trends in left and right thalamic volumes and alpha peak frequency. We did not find evidence here that sex or socioeconomic status impacted alpha peak frequency in either group.

One of the main findings of our study is that individuals with PAE/FASD have reduced alpha peak frequency when compared to TDC, and the group difference is particularly pronounced in late childhood and adolescence. Reduced alpha peak frequency in FASD is not surprising given that average alpha power is similarly reduced in children with FAS between 8-12 years of age (Candelaria-Cook et al., 2021). Also, lower alpha power has been seen in adult participants whose parents had an alcohol use disorder (Finn and Justus, 1999). Interestingly, in infancy higher spectral power is seen in infants born to mothers with alcohol use disorders (Havlicek et al., 1977, Chernick et al., 1983), lasting up to 4-6 weeks of age (Ioffe et al., 1984), and 6 months of age (Stephen et al., 2018). The higher spectral power in alpha and beta frequency bands (9.57-17.48 Hz) is particularly pronounced in infants of mothers who binge drank, suggesting intermittent ingestion of large quantities of alcohol might be more harmful than continuous chronic exposure (Ioffe and Chernick, 1988). While our data show a bit of variation among PAE/FASD participants, it is unclear if differences may be related to sub-diagnoses (FAS, pFAS, or ARND), amount of alcohol consumed, timing of alcohol consumption during pregnancy, or key developmental processes within alpha oscillations to which prenatal alcohol exposure may selectively disrupt or delay. In the current study, we found elevated alpha peak frequencies in infancy, but reduced alpha peak frequencies in adolescence. Given the upper age limit of our study was 17 years of age, it remains uncertain if the alpha peak deficit seen in FASD persists into adulthood or is a developmental delay. In the autism literature, it is not uncommon for alpha peak frequency changes to parallel spectral power findings (Edgar et al., 2019, Edgar et al., 2015). Therefore, the two spectral qualities (average power and peak frequency) may be directly related, and if so, it is possible the deficit seen in children with an FASD may persist into adulthood. Furthermore, the reduction of alpha peak frequency in the parietal/occipital region is in line with research showing alcohol influences these regions (Rosen et al., 2014, Lewis et al., 2016). In adolescents with FASD, we did not find the typical age-related increase in alpha peak frequency, similar to (Lebel et al., 2012) who also found heavy PAE resulted in a loss of age-appropriate volume increases in parietal and occipital regions.

Typically, alpha peak frequency shifts from lower to higher frequencies during development (Miskovic et al., 2015, Edgar et al., 2019, Somsen et al., 1997), reaches its maximum in adolescence, and then gradually decreases as a function of age. Here, we found similar results that alpha peak frequency increases with age in childhood and adolescence in TDC. While a quadratic linear trend typically captures the relationship across the lifespan, a linear trend best described the relationship given the age of our sample. It has been shown that by 10 months of age, 6-9 Hz alpha peaks can be detected in posterior alpha rhythms (Marshall et al., 2002), which is a range similar to the alpha peak frequencies found here.

White matter structure is a key determinant of alpha peak frequency (Valdés-Hernández et al., 2010, Jann et al., 2012). It has been suggested that increases in alpha peak frequency may be related to developmental changes in white matter, elimination of active synapses (Whitford et al., 2007), or an increase in myelination or axon size (Segalowitz et al., 2010). Here, we explored relationships between alpha peak frequency and total white matter volume and found that in the combined sample, higher alpha peak frequencies were positively correlated to higher cerebral white matter volumes. Furthermore, within TDC higher alpha peak frequencies were correlated to more total cerebral white matter volume, but not within PAE/FASD. Although we did not find evidence of a relationship between thalamic structure and alpha peak frequency in the current study, we found a few group specific trends in left and right thalamic volumes and alpha peak frequency. Specifically, in TDC, higher alpha peak frequencies were correlated to larger right thalamus volume, while in PAE/FASD higher alpha peak frequencies were correlated with smaller left thalamus volume. It is important to note that these analyses each utilized a smaller subset of data and, as such, may not be sufficiently powered and/or the effect sizes are small to moderate. Also due to the fact that multiple brain structures were explored simultaneously we had to correct for multiple comparisons between structures, which reduced the ability to make stronger conclusions on the relationship between thalamic structure and alpha peak frequency in this sample. Others have found relationships between thalamic structure and alpha peak frequency in TDC individuals, in the absence of a correlation group difference between TDC and ASD (Green et al., 2022). Alpha oscillations are thought to have both thalamic and cortical generators. Alpha peak frequency is negatively correlated with a tissue property (the intracellular volume fraction) of the optic radiation, a white matter tract connecting the lateral genicular nucleus and primary visual cortex, further demonstrating integrity of the thalamic nuclei and early visual areas are integral in determining individual alpha peak frequency (Minami et al., 2020). It remains possible that a larger sample size and/or more direct thalamus hypothesis testing would find significant relationships between alpha peak frequency and thalamic structure.

We did not find evidence of a sex difference in alpha peak frequency in either TDC or PAE/FASD. Similarly, by ages 10-12 years, others have reported no sex differences in alpha peak frequency, even though males demonstrate higher alpha power than females (Cragg et al., 2011). Males often show more alpha power than females (Barry and Clarke, 2009) between 8-12 years (Clarke et al., 2001) and ages 10-13 years (Cragg et al., 2011). However, the relationship is typically linked to advanced pubertal stage in males (Howsley and Levita, 2018). In a recent study, males (9-15 years of age) had higher alpha power in the left dorsal prefrontal cluster (Ott et al., 2021) along with frequency specific changes in global normalized power (Candelaria-Cook et al., 2022). We also did not find any evidence of a PAE and sex interaction. While PAE resulted in an impaired alpha peak frequency, the results were consistent across sex and did not support sexually dimorphic differences, similar to (Panczakiewicz et al., 2016, Candelaria-Cook et al., 2021).

Research has found alpha peak frequency to be a stable neurophysiological trait marker of global structural and functional properties of the brain in healthy adults and not easily modifiable by cognitive interventions (Grandy et al., 2013). While we did not explore relationships between alpha peak frequency and behavioral measure in this study, research suggests alpha peak frequency is related to several behavioral measures. In infants 12-36 months of age, alpha peak frequency is correlated to non-verbal cognitive ability, but not verbal ability in infants at low and high risk of ASD (Carter Leno et al., 2021). In preschool age children, alpha peak frequency is positively correlated with sensorimotor abilities, but not cognitive processing speed or visual working memory function (Mierau et al., 2016). In younger children, a fast processing speed was associated with a higher alpha peak frequency (Edgar et al., 2019). Lower alpha peak frequency may indicate deficits in the thalamocortical networks and/or cortico-cortical networks. When compared to average alpha power, alpha peak frequency may be a more sensitive and reliable measure of alpha band development (Levin 2020). In typical development and in adulthood, alpha spectral power has good test-retest

reliability and excellent split-half reliability (Candelaria-Cook et al., 2022, Candelaria-Cook et al., 2020); therefore, it is possible alpha peak frequency may also have good to excellent reliability.

There were several limitations which warrant caution when considering these results. First, data were combined across 5 different studies spanning 13 years of research. As such, there is heterogeneity in resting-state task design. Efforts were made to harmonize data, while including as much data as possible. For example, while eyes-open resting-state may not be the preferred state for examining alpha oscillations, it was used due to the fact that all 5 studies had eyes-open data. Furthermore, the amount of data available in an eyes-open state varied by individual study. We decided to include all available eyes-open data to maximize sample size. In the reported sample, the alpha peak was clearly discernible in the eyes open resting-state. To equalize the different task lengths, we maintained an epoch size of 2 seconds throughout, used the same post-epoch processing pipelines, and compared data quality between studies, see Table 1. We did not find evidence that resting-state task length contributed to reported group differences found. Second, in the various independent studies, there were individuals with prenatal alcohol exposure who may have had concurrent exposure to other substances. Due to the retrospective study design in 4 of the 5 studies included in this analysis, we were unable to exclude or control for concurrent polysubstance use; therefore, a confounding effect of other substances could not be examined and requires careful attention in future studies. Third, the age range of children included in this analysis spans from 6 months to 17 years. A serial cross-sectional design and hierarchical linear regression analyses limit complete understanding of age-related changes in alpha peak power over time. Linear trends were used in this analysis, although previous research has found spectral changes across the lifespan follow a quadratic relationship with peaks around the fifth or sixth decade of life (Gómez et al., 2013). Linear trends were used here based on the age range of the current sample (6 months to 17 years). During childhood and adolescence, alpha spectral changes increase with age in a linear fashion. We currently have no information on PAE effects on alpha peak frequency in adulthood to offer better characterization of alpha peak differences. Future research would benefit from longitudinal studies examining a broader age range. Fourth, SES can be a confounding variable in PAE/FASD clinical studies. Low SES alone can have an adverse effect on brain development and may be contributing to alpha peak deficits currently observed. While we did not observe significant correlations between alpha peak frequency and SES here, either within each group or in the overall sample available, our sample size was limited to select datasets which collected SES. Fifth, it is important to note that the infant data used here is a subset of available data. While we screened 78 datasets, just 22 datasets had a single peak within the 6 to 13 Hz alpha band. It may be that the infants who are good alpha generators later in life, show early stable alpha peaks, but are not representative of most 6m olds. Despite these limitations, the current study had several strengths including a large sample size for PAE/FASD research, combined data analysis from 5 individual studies which were each age and group matched, and a novel approach to examining alpha peak frequency in sensor MEG data. Furthermore, while data from 5 studies were combined, it is important to note that all 5 studies were conducted by the same research group using the same MEG scanner and study site. Due to the fact that all studies had eyes-open resting-state data available, we combined data, even though broader study aims may have differed.

5 Conclusions

Our results indicate that alpha peak frequency might be impaired in infants, children, and adolescents with PAE/FASD. By late adolescence alpha peak frequency is significantly reduced in individuals with an FASD or PAE, whether this deficit represents a long-term deficit is unknown, although our data suggest group differences between TDC and PAE/FASD persist throughout development. Our results also indicate that higher alpha peak frequencies are correlated to more total cerebral white matter volume in TDC, but not within PAE/FASD. Group specific trends in left and right thalamic volumes and alpha peak frequency warrant future investigation. While we

explored relationships with other variables, we did not find evidence that alpha peak frequency had significant relationships with sex or socioeconomic status in this sample. Reduced alpha peak frequency in development as observed here is an example of the detrimental impact prenatal alcohol exposure can have on neurophysiological processes.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Declaration of Competing Interest

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

The original contributions generated for the study are included in the article, further inquiries can be directed to the corresponding author. The raw data cannot be shared publicly as they are considered identifiable data and cannot be shared according to the guidance of The Institutional Review Board of the University of New Mexico. With appropriate IRB protocol in place, data for this study can be requested at the discretion of the corresponding author through the COINS data exchange.