



Examining the effects of prenatal alcohol exposure on corticothalamic connectivity: A multimodal neuroimaging study in children

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ABSTRACT

Children with a fetal alcohol spectrum disorder (FASD) experience a range of cognitive and behavioral effects. Prior studies have demonstrated white matter changes in children with FASD relative to typically developing controls (TDC) and these changes relate to behavior. Our prior MEG study (Candelaria-Cook et al. 2020) demonstrated reduced alpha oscillations during rest in FASD relative to TDC and alpha power is correlated with behavior. However, little is known about how brain structure influences brain function. We hypothesized that alpha power was related to corticothalamic connectivity. Children 8–13 years of age (TDC: N = 25, FASD: N = 24) underwent rest MEG with eyes open or closed and MRI to collect structural and diffusion tensor imaging data. MEG spectral analysis was performed for sensor and source data. We estimated mean fractional anisotropy in regions of interest (ROIs) that included the corticothalamic tracts. The FASD group had reduced mean FA in three of the corticothalamic ROIs. FA in these tracts was significantly correlated with alpha power at the sensor and source level. The results support the hypothesis that integrity of the corticothalamic tracts influences cortical alpha power. Further research is needed to understand how brain structure and function influence behavior.

1. Introduction

Children with a fetal alcohol spectrum disorder (FASD) can experience a range of physical, cognitive, and behavioral effects due to prenatal alcohol exposure (PAE) (Mattson et al., 2010, 2013). The effects of PAE on brain development vary depending on the pattern of alcohol consumption (Cantacorps et al., 2018; Delatour et al., 2018), the gestational age of the fetus at the time of exposure (Savage et al., 2002; Stephen et al., 2018), and the amount of alcohol consumed by the mother (Goodlett and Eilers, 1997). One robust finding across varying levels of maternal alcohol consumption is impairment in attention abilities of the offspring (Coles, 2001; Kodituwakku et al., 2011; Kodituwakku et al. 2001; Lees et al., 2020; O'Malley and Nanson, 2002). Recently a report from the Adolescent Brain and Child Development (ABCD) study indicates that even otherwise typically developing children with PAE experience persistent attention deficits relative to the unexposed group (Lees et al., 2020). However, the underlying mechanism that leads to impaired attention in children with an FASD remains

unknown.

Alpha oscillations, measured using neurophysiological techniques (MEG/EEG), are observed during rest and vary in strength during performance of certain tasks (Clayton et al., 2018). Alpha oscillations have been considered a marker of an idling brain (Lundqvist et al., 2013; Pfurtscheller et al., 1996), as seen by the increase in alpha oscillations in the parietal cortex in individuals who are awake but resting with their eyes closed. Alpha reactivity, the difference in alpha power during eyes-closed and eyes-open states, has also been shown to relate to brain health with systematic differences in alpha reactivity being reported across a broad range of clinical populations (Ciesielski et al., 2007; Cornew et al., 2012; Hassan et al., 2017; Stam et al., 2005) and indicates that alpha power may reveal different patterns between groups depending on state. Alpha oscillations tend to increase in regions of cortex where incoming stimuli are intended to be ignored (Bazanava and Vernon, 2014; Mazaheri et al., 2014). For example, in a multisensory selective attention task, alpha oscillations increased over auditory cortex when the visual cue was to be attended (Mazaheri et al., 2014).

Abbreviations: FASD, fetal alcohol spectrum disorders; FAS, fetal alcohol syndrome; PAE, prenatal alcohol exposure; CC, corpus callosum; CST, corticospinal tract; PIC, posterior limb of the internal capsule; AIC, anterior limb of the internal capsule; CTR, corticothalamic radiation; MEG, magnetoencephalography; DTI, diffusion tensor imaging; FA, fractional anisotropy; TDC, typically developing controls; SES, socioeconomic status; BRIEF, Behavioral rating inventory of executive function.

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Furthermore, visual spatial attention tasks demonstrate a lateralized response with increased alpha oscillations observed in the hemisphere corresponding to the unattended hemifield (ter Huurne et al., 2013). Finally, children with attention deficits experience reduced lateralization of these alpha oscillations that also corresponds with poorer ability to ignore distracting stimuli (ter Huurne et al., 2013). These studies support the role of alpha oscillations in directing attention to task-salient stimuli.

The generators of alpha oscillations remain poorly understood, but preclinical and clinical studies support the role of the thalamus in generating resting alpha oscillations (Hughes et al., 2011; Hughes and Crunelli, 2005; Lorincz et al., 2009; Ohmoto et al., 1978) with thalamic pacemaker neurons proposed to be driving cortical alpha oscillations (Jahnsen and Llinas, 1984). Specifically, thalamocortical neurons in lamina A and A1 of the lateral geniculate nucleus fire when cortical alpha activity is observed (Hughes et al., 2002, 2004). Preclinical studies demonstrated a marked decrease in cortical alpha with thalamic lesions whereas other studies have indicated a strong correlation between thalamic neural spike rate and phase of cortical alpha oscillations (Lorincz et al., 2009). Furthermore, noninvasive studies have demonstrated a relationship between thalamic volume and alpha peak frequency, another parameter that defines alpha oscillations (Edgar et al., 2015). On the other hand, alpha oscillations that are mediated by top-down attention are often considered to be generated in cortex (da Silva et al., 1973, 1991). Therefore, while thalamus appears to play a role in generating cortical alpha oscillations, it does not appear to be the only generator of alpha oscillations. These studies support the role of thalamocortical connectivity in the generation of alpha. Our recent studies provide evidence for impaired attention (Pinner et al., in preparation) in children with an FASD and reduced alpha power (Candelaria-Cook et al., 2020) in children with fetal alcohol syndrome (FAS) relative to typically developing controls. The Candelaria-Cook et al. (2020) study postulated the reduction in alpha power was attributed to reduced connectivity between posterior brain regions and the thalamus, although the connectivity between thalamus and cortex was not directly assessed.

With some exceptions, prior literature indicates reduced white matter integrity in PAE with developmental patterns being altered in children with PAE (Fan et al., 2016; Green et al., 2013; Lebel et al., 2008; Sherbaf et al., 2019) along with associations between DTI and MEG signals (Pinner et al., 2020). The earliest reports found a reduction in the volume of the corpus callosum (Riley et al., 1995). Recent studies have employed diffusion tensor imaging (DTI) to examine changes in white matter integrity in children with PAE as reviewed by (Sherbaf et al., 2019). The most prominent finding is reduced fractional anisotropy (FA) in callosal white matter tracts. However, the changes in white matter are not limited to corpus callosum. In a whole brain analysis of DTI, Fan et al. (2016) reported white matter tracts that differed in either fractional anisotropy or mean diffusivity in children with PAE versus typically developing children, and multiple regression analysis determined that these alterations partially mediated the information processing abilities of children with PAE. Similarly, Paolozza et al. (2017) reported differences in FA in multiple tracts in children with PAE versus unexposed children, including corticospinal tract. Also, FA was related to eye movement control in unexposed children but not in the PAE group. These results support the general finding that white matter tracts are impacted by PAE and also relate to behavioral measures.

In addition to relating white matter integrity to behavior, a few studies have examined the relationship between brain structure and function (O'Conaill et al., 2015; Pinner et al., 2020; Santhanam et al., 2011; Wozniak et al., 2011). For example, Wozniak et al. (2011) demonstrated that interhemispheric functional cortical connectivity as assessed with fMRI is correlated with white matter integrity of the corpus callosum indicating that white matter deficits are likely to impede synchronization of different brain regions. Our recent study using a data-driven analysis approach extends these findings by

reporting a link between sensory function as assessed with MEG with changes in fractional anisotropy in cerebellum (Pinner et al., 2020). Less is known about the role of corticothalamic connectivity in FASD as this has not been a region specifically examined in this population (Sherbaf et al., 2019) to the best of our knowledge. Based on our prior study demonstrating reduced alpha power during rest in children with FAS relative to typically developing children, we hypothesized that corticothalamic connectivity would be altered in children with an FASD and this would in turn relate to alpha power during rest.

In our recently published results (Candelaria-Cook et al., 2020), we identified a difference in alpha power in children with FAS relative to typically developing children (TDC). To assess the role of corticothalamic connectivity in generating alpha oscillations in children with an FASD relative to TDC, we extended the prior results (Candelaria-Cook et al., 2020) using an overlapping sample to employ a multimodal approach using MEG to measure alpha normalized power at the sensor and source level and DTI to measure white matter integrity. Examining correlations at the sensor and source level allows us to determine the generalizability of the findings to the minimally processed sensor level data and is thus relevant to EEG studies that do not perform source analysis. We hypothesized that corticothalamic tracts would reveal reduced fractional anisotropy (FA) in children with an FASD relative to typically developing children and that FA in these corticothalamic tracts would be significantly correlated with the strength of the alpha oscillations measured with MEG. We further hypothesized that attention measures would correlate with FA measures as a direct link between white matter connectivity and attention performance in children.

2. Methods

2.1. Participants

We recruited 49 children (8–13 years) and their parents to participate in a study that was designed to examine attention deficits in children with an FASD. At the first visit, the study procedures and study risks were explained to the family. Once all questions were answered, the families were given time to review the consent form, discuss the study, and then were asked to sign the consent and assent forms to continue participation in the study. The study was approved by the University of New Mexico Health Sciences Center Human Research Review Committee and was in accordance with the ethical standards established by the 1964 Helsinki declaration and the subsequent modifications. The sample represented a diverse population with the following demographics (32% non-Hispanic white, 12% Hispanic, 40% Native American, 2% African American, 2% Pacific Islander, 2% Asian and 10% unreported).

Children with an FASD were recruited from the prenatal exposures clinic. All children were evaluated by a multidisciplinary team, and the FASD diagnostic category was determined by consensus diagnosis. The evaluation included assessment of facial features and growth by a pediatrician, as well as assessment of the child's cognitive and behavioral functioning by a pediatric neuropsychologist and behavioral specialist. The research designation of FASD was performed following the diagnostic criteria laid out by Hoyme et al. (2016). Children were designated as alcohol-related neurodevelopmental disorder (ARND), partial fetal alcohol syndrome (PFAS) or fetal alcohol syndrome (FAS). Additional details are provided in Candelaria-Cook et al. (2020).

Typically developing children (TDC) were recruited from the community. TDC had no known developmental or neurological disorders and no reported prenatal alcohol exposure based on maternal self-report. Children with any reported exposure to PAE based on maternal interview were excluded from the TDC group.

All participants scored above a standard score of 70 on either the verbal comprehension or perceptual reasoning composite score IQ metrics (WASI II) or were excluded (1 FASD participant). Parents completed the Behavioral Rating Inventory of Executive Function (BRIEF) (Gioia et al., 2000) and the Conners 3 parent questionnaire

(Conners, 2008) to assess executive function and attention deficits in these children.

2.2. Task

Data were collected during a resting state MEG task in which participants were instructed by recorded verbal instruction to blink at pre-defined intervals and open or close their eyes for assessment of alpha power during both eyes open and eyes closed states. Blinks were recorded at the beginning of each rest segment to provide well-characterized eye blinks for the purpose of eliminating eye-blink artifact from the data. The resting paradigm consisted of two 30 s segments of eyes closed interleaved with one 60 s segment of eyes open. The participant was requested to rest quietly throughout without thinking about anything in particular. During the eyes open condition the participant was asked to focus on a fixation cross presented on a back-projection screen placed 100 cm in front of the participant. This design was implemented for use in MEG clinical trial studies and allows for assessment of resting spectral power as well as alpha reactivity to examine resting parieto-occipital alpha oscillations. Alpha spectral power was estimated from the resting state paradigm.

2.2.1. MEG

MEG data were collected using an MEGIN Neuromag 306 channel biomagnetometer which consists of 204 planar gradiometer sensors and 102 magnetometer sensors located around the head. Data were digitized at 1000 Hz and an online anti-aliasing filter of 300 Hz and a high pass filter of 0.1 Hz were applied during data collection. The MEG session consisted of a go/nogo paradigm, a prosaccade paradigm and a resting state paradigm and lasted approximately 1 h.

MEG analysis was performed as described in Candelaria-Cook et al. (2020). Briefly, resting data were initially processed through the Neuromag Maxfilter software to remove noise and correct for head movement during the scan. For sensor level analysis all data were registered to a common head position across participants chosen based on the average head position of the study participants. The Maxfiltered data were further processed to remove eye blink and heartbeat artifact using the signal space projection function available in the MNE python package (Gramfort et al., 2013). The continuous data were then divided into 2 s epochs and sorted into eyes open or eyes closed conditions. Epochs in which the magnetic field exceeded 5 pT were rejected due to artifact. For sensor level analysis, the epochs were run through a custom Matlab script which calculated the power spectrum of each epoch and then provided an average power spectrum across all epochs for each participant. The data at each sensor were summarized into the physiological frequency bands with alpha power defined as 8–13 Hz. Spectral power was summarized into regional (frontal, temporal, central, parietal and occipital) and global estimates of alpha power by averaging alpha power across channels. These estimates were based on the planar gradiometers only to provide an estimate of spectral power that was maximal under the sensor group. For source based analysis, the surface-based cortical parcellation obtained from Freesurfer based on each participant's T1-weighted MRI sequence was used to identify the source space for inverse modeling. Source analysis was performed using the anatomically constrained dynamic statistical parametric model available in MNE-python to obtain cortical surface based source estimates. The regularization parameter was set at 3 and source orientation constraint parameter was set at 0.2. The result was a z-score estimate for defining whether each voxel differed significantly from empty room values. Power spectral estimates were obtained using the MNE-python Discrete Prolate Spheroid Sequence using 7 tapers at 4 Hz. Normalized power was estimated for each of the 62 regions defined by the DKT atlas, by calculating the average spectral power across voxels for each region. Spectral power was normalized by dividing the power at a given frequency by the total power across the 1–58 Hz range. Global spectral power was obtained by averaging spectral power by frequency across all

regions and regional spectral power was obtained by averaging across lobe-specific regions of the DKT atlas. The data were summarized into the physiological frequency bands with alpha power defined as 8–13 Hz. Spectral power within these regions was calculated and exported to SPSS for statistical analysis.

2.3. MRI/DTI acquisition

A structural T1 image was obtained using the 3 T Trio Tim Siemens scanner for source analysis and registration of the DTI data. In addition, diffusion tensor imaging was performed to capture white matter microstructure. Sagittal T1-weighted anatomical images were obtained with a multi-echo 3D MPRAGE sequence TR/TE/TI = 2530/1.64, 3.5, 5.36, 7.22, 9.08/1200 ms, flip angle = 7°, field of view (FOV) = 256 × 256 mm, 1 mm isotropic. The DTI was collected in 4 separate runs with anterior to posterior and posterior to anterior data collection. FOV was 224 × 224, resolution 2.0 mm isotropic, flip angle 84/157, TE = 108 ms, TR = 4000 ms, multi-band factor = 3, with 72 slices acquired. B-value was 2400 s/mm² with 44, 47, 42 and 40 independent directions collected across the four runs.

2.4. DTI analysis

DTI data were processed using the standard FSL analysis pipeline as described previously (Sanfratello et al., 2017). Briefly, this includes correction of susceptibility artifacts using TOPUP, eddy current correction using EDDY, tensor fitting using DTIFIT and registration to standard space. White matter tracts were identified using the TBSS parameters and average FA values of the regions of interest were extracted from the resulting TBSS skeletonized maps using the JHU-ICBM-DTI-81-White-Matter-defined regions of interest (ROIs). From this atlas the tracts that were chosen to evaluate corticothalamic connectivity were: corticospinal tract (CST), anterior limb of the internal capsule (AIC), posterior limb of the internal capsule (PIC) and the posterior thalamic radiations (PTR). Tracts from both the left and right hemisphere were evaluated. Based on the consistent reporting of corpus callosum (CC) results in FASD, we included this tract in the analysis for comparison purposes. The use of TBSS helped to account for possible volume and structural changes associated with PAE.

2.5. Statistical analysis

Demographic variables were compared between groups using either a two-sample *t*-test for continuous variables or a χ^2 test for categorical variables (sex). Multivariate analysis of variance (MANOVA – Pillai's trace) of DTI tracts was performed to determine if there were significant group differences in FA between children in the FASD and TDC groups. The tracts that revealed significant group differences were then examined to determine if mean FA in these tracts related to a priori comparisons of global alpha power or parietal/frontal regional alpha power. Multiple comparison correction was performed using false discovery rate (FDR) correction (Benjamini and Hochberg, 1995). Pearson correlations between FA and MEG alpha power were examined at the sensor and source level. Differences in correlation between groups were tested using an *r*-z transformation. Outlier analysis of the white matter values led to the loss of data from one participant with FASD for PIC-R. Outlier analysis for MEG sensor data led to the loss of one additional participant with FASD and one TDC in the correlation analysis. Statistical analysis was performed using SPSS v20.

3. Results

The sample overlaps with the prior study (Candelaria-Cook et al., 2020) which reported group differences in alpha power in children with FASD compared to TDC. Here we use the global and regional source spectral analysis reported in our prior work and add the analysis of

specific DTI tracts to examine how MEG spectral power relates to white matter tract integrity assessed with DTI. We did not successfully obtain MRI data from all participants, thus the sample included in this analysis is comprised of 49 of the 51 participants included in (Candelaria-Cook et al., 2020). The sample is well-matched on sex ($p > 0.3$) and age ($p > 0.6$), but differences in SES and on behavioral measures were observed with the FASD group having a lower SES relative to TDC and overall poorer performance on behavioral measures. The BRIEF and Connors scores are t-scores with a mean of 50 representing normal performance and scores greater than 65 representing clinically meaningful differences. The sample characteristics are shown in Table 1.

Socioeconomic status was included in the initial multivariate model to determine if it influenced the group comparison. SES did not reveal a significant relationship with fractional anisotropy (FA) values (p 's > 0.2); therefore SES was removed from the model. The univariate results of the MANOVA for the FA tracts tested (Fig. 1) are shown in Table 2 and tracts with group differences are shown in Fig. 2. Using Pillai's trace, there was a significant effect of group across the white matter tracts, $V = 0.38$, $F(9,38) = 2.58$, $p = 0.02$. Three of nine tracts tested revealed significant group differences in mean FA: AIC-L, PIC-R and PIC-L. In all three tracts, TDC revealed greater mean FA than the FASD group. Consistent with ongoing neurodevelopment, we also found a significant positive correlation between mean FA and age in two of the tracts (PIC-L $-r = 0.143$, $p = 0.327$, PIC-R $-r = 0.48$, $p = 0.001$, AIC-L $-r = 0.46$, $p = 0.001$).

The tracts that revealed significant group differences were tested to examine if mean FA was associated with resting alpha power during eyes open or eyes closed states (see Table 3; Fig. 3A). Associations between alpha power and SES were also examined and found not to be significant (p 's > 0.05). Values in bold represent significant correlations after FDR correction. Global normalized alpha power was significantly correlated with mean FA across both groups in both left and right hemispheres. PIC-R revealed significant correlations with global alpha power across all participants as well as in the TDC alone for open and closed condition and with parietal alpha closed conditions; although the FASD group did not reveal a significant correlation, the correlation value was not significantly different than TDC in any case ($p > 0.05$). Correlations with frontal and parietal regions were assessed based on the connectivity pattern of the PIC and AIC tracts; the PIC tract connects to sensorimotor cortex and parietal cortex, whereas AIC connects anterior thalamus to the anterior cingulate and prefrontal cortex (Wycoco et al., 2013). The only tract and functional pairing that did not show a significant correlation was the AIC-L for the eyes open condition for global, normalized alpha power.

Similar to the sensor level results, there was a significant correlation between source level normalized alpha power in frontal and parietal regions and mean FA in PIC-R, PIC-L and AIC-L tracts (see Table 4; Fig. 3B). Based on the strong projections in the PIC to sensorimotor cortex, we examined the relationship between FA and alpha power in precentral regions and again found a strong positive correlation in both left and right PIC. Overall, the correlations were stronger in right vs. left hemisphere with the exception of precentral cortex. Again, there were

no significant differences in correlation value between groups.

Finally, we examined if mean FA was related to behavioral measures obtained in this group of children. There were no significant correlations in the group overall or in either group separately between mean FA and Connors inattention or BRIEF scores (p 's > 0.2).

4. Discussion

The results of this study demonstrate a decrease in fractional anisotropy (FA) in corticothalamic tracts in children with an FASD relative to typically developing controls. Tracts that revealed group differences showed a significant correlation between corticothalamic integrity as assessed by mean FA and normalized alpha power as assessed with MEG measured during the resting state with both eyes open and eyes closed. Prior studies have independently demonstrated deficits in white matter in children with an FASD (Sherbaf et al., 2019) and altered brain function as assessed with MEG (Candelaria-Cook et al., 2020; Coffman et al., 2020; Coffman et al., 2013; Stephen et al., 2012; Tesche et al., 2015). However, to the best of our knowledge, only one study from our group examined the link between structure and function using DTI and task-based MEG activations (Pinner et al., 2020). We have not yet reported associations between DTI and resting MEG measures. This result provides multimodal evidence for one possible mechanism for impaired brain function in children with an FASD.

The significant correlations between mean FA and normalized alpha power across groups reveal that children with lower alpha power were also the children with reduced mean FA regardless of group. Despite overlap between groups, individuals in the FASD group tended to have lower alpha power, as reported by Candelaria-Cook et al. (Candelaria-Cook et al., 2020), as well as lower FA values relative to TDC. This linear relationship across groups provides support for viewing this association as a way to explain individual differences in brain function (Pitchford and Arnell, 2019). Unfortunately, the current sample of participants did not allow us to obtain a meaningful estimate of prenatal alcohol exposure because participants were recruited at 8–13 years of age and some participants were adopted. In most instances, recall of dose information was unavailable due to the length of time that had passed between pregnancy and study enrollment (8–13 years), along with lack of direct access to the biological mother in the case of adoption. This limited our ability to further assess whether the linear relationship is directly related to amount of alcohol consumed during pregnancy. The result supports our hypothesis that alpha power is related to corticothalamic connectivity. However, the current results did not support a direct correlation between corticothalamic connectivity measured with DTI and the behavioral measures reported here. It is important to note that both of the child behavior measures were based on parental report rather than direct assessment of attention (Connors, 2008; Gioia et al., 2000). While the assessments provide information on executive functioning and attention, parental report is expected to be less sensitive than neuropsychological assessments of specific aspects of attention. Additional studies that more directly assess attention function using neuropsychological measures may better determine if alpha power and corticothalamic connectivity are related to specific types of attention in children.

As described above, the thalamus is a primary driver of resting alpha oscillations (Hughes and Crunelli, 2005; Hughes et al., 2011). The correlation between white matter integrity in corticothalamic tracts and resting alpha power provides additional support to this prior literature base. Despite a relatively broad literature supporting the role of thalamus in driving resting alpha oscillations, to the best of our knowledge, this is the first report demonstrating a structure/function link between thalamus and alpha power in children with an FASD. However, there is a recent report in TDC and children with autism linking thalamic volume with resting alpha peak frequency (Edgar et al., 2015), providing additional support for the cortico-thalamic link in mediating alpha oscillations broadly. The current results are consistent with ongoing

Table 1
Sample characteristics.

	TDC (N = 25)	FASD (N = 24)
Age (years)	10.2 (0.32)	10.3 (0.33)
Gender (M(%)/F(%))	11(44)/14(56)	8 (33)/16(67)
Barratt SES (1–66)	50.7 (1.9)	30.9 (2.4)**
BRIEF - GEC	50.2 (2.1)	67.4 (2.2)**
BRIEF - Beh Reg	49.1 (2.0)	66.5 (3.2)**
BRIEF - Metacog	52.2 (2.4)	67.2 (1.9)**
Connors - Inattention	51.6 (2.0)	73.4 (2.2)**

SES: socioeconomic status; BRIEF: GEC – Global executive composite score, Beh Reg – behavioral regulation, Metacog – metacognition.

** $p < 0.001$

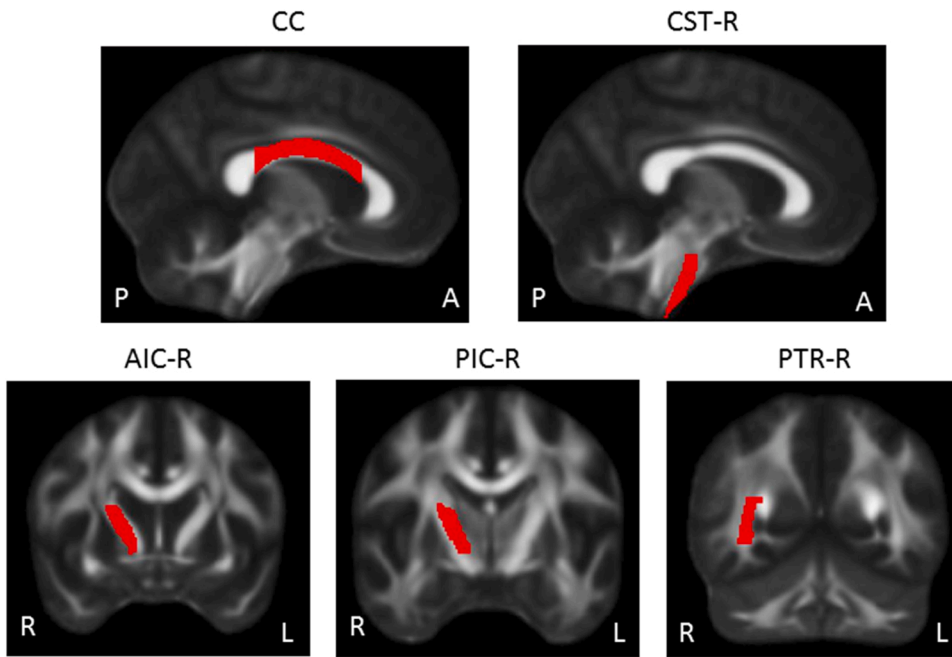


Fig. 1. Regions of interest of fractional anisotropy (FA) measures. Right hemisphere ROIs are shown, homologous left hemisphere regions were also examined with the exception of corpus callosum where midline values were obtained. It is important to note that we obtained FA estimates from the white matter skeleton identified with TBSS, reducing the potential confound of the effects of volume effects (Smith et al., 2006). CC- corpus callosum, R/L – right/left, CST – corticospinal tract, AIC – anterior limb of the internal capsule, PIC, posterior limb of the internal capsule, PTR, posterior thalamic radiations.

Table 2
Estimated marginal means (standard error) of FA values for corticothalamic tracts.

Tract	TDC	FASD	p-value, eta ²
CC	.587 (0.009)	.578 (0.01)	.515, 0.010
CST-R	.438 (0.014)	.437 (0.015)	.953, < 0.001
CST-L	.455 (0.009)	.462 (0.009)	.588, 0.007
AIC-R	.537 (0.006)	.522 (0.007)	.112, 0.057
AIC-L*	.513 (0.005)	.489 (0.005)	0.001 , 0.224
PIC-R*	.664 (0.005)	.646 (0.005)	0.011 , 0.137
PIC-L*	.658 (0.004)	.640 (0.004)	0.004 , 0.170
PTR-R	.538 (0.005)	.526 (0.006)	0.107, 0.058
PTR-L	.544 (0.006)	.537 (0.006)	.475, 0.012

CC – corpus callosum, R/L – right/left hemisphere CST– corticospinal tract, AIC – Anterior internal capsule, PIC – posterior internal capsule, PTR – posterior thalamic radiation.

* p < 0.05

Table 3
Sensor-level correlations between ROI mean FA and normalized alpha power - r (corrected p-value) N.

	All TDC FASD	PIC-R - RH	PIC-L - LH	AIC-L - LH
Global open	0.285 (0.058) 47	0.492 (0.006) 46	0.326 (0.034) 47	0.285 (0.058) 47
	0.608 (0.019) 24	0.196 (0.391) 24	0.331 (0.161) 24	0.331 (0.161) 24
Global closed	0.256 (0.602) 22	0.511 (0.01) 46	0.429 (0.011) 47	0.352 (0.024) 47
	0.583 (0.02) 24	0.271 (0.636) 23	0.065 (0.824) 23	0.065 (0.824) 23
Parietal alpha open	0.325 (0.67) 22	0.423 (0.012) 46	0.342 (0.028) 47	0.130 (0.687) 23
	0.505 (0.053) 24	0.389 (1.0) 23	0.422 (0.09) 24	0.422 (0.09) 24
Parietal alpha closed	0.209 (0.616) 22	0.492 (0.007) 46	0.391 (0.015) 47	0.498 (0.055) 24
	0.591 (0.024) 24	0.249 (0.278) 24	0.389 (0.114) 24	0.389 (0.114) 24
Frontal alpha open	0.317 (0.679) 22	0.252 (0.611) 23	0.284 (0.618) 23	0.329 (0.033) 47
				0.270 (0.250) 24
Frontal alpha closed				0.223 (0.599) 23
				0.386 (0.017) 47
			0.386 (0.115) 24	
			0.247 (0.594) 23	

development of white matter tracts in children up to 17 years of age (Alkanyi et al., 2011). Finally, the difference in white matter tract integrity reported here is consistent with rodent studies reporting damage to the corticothalamic loop with PAE (Granato et al., 1995; Minciacchi et al., 1993).

Because parietal alpha oscillations are more prominent during the eyes closed condition, we posited that the structure/function relationship would be more robust during the eyes closed condition. While both eyes closed and eyes open conditions revealed significant correlations, regional and global analysis revealed a consistently stronger correlation in the eyes closed condition, as expected. This pattern was more variable when examining individual regions of interest from the DKT atlas suggesting that signal to noise drops as the region size becomes smaller. However, the differences in eyes open and eyes closed were not significant. This is consistent with our prior study showing similar patterns across eyes open and eyes closed conditions in resting alpha power (Candelaria-Cook et al., 2020) providing further evidence for the generalized role of white matter tract integrity in alpha power

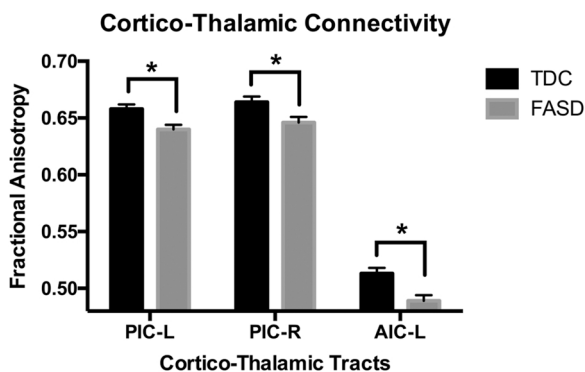


Fig. 2. Mean FA values for the ROIs that revealed significant group differences between TDC and FASD groups. PIC-L – posterior limb of the internal capsule – left hemisphere, PIC-R PIC – right hemisphere & AIC-L, anterior limb of the internal capsule – left hemisphere. Error bars denote standard error of the mean.

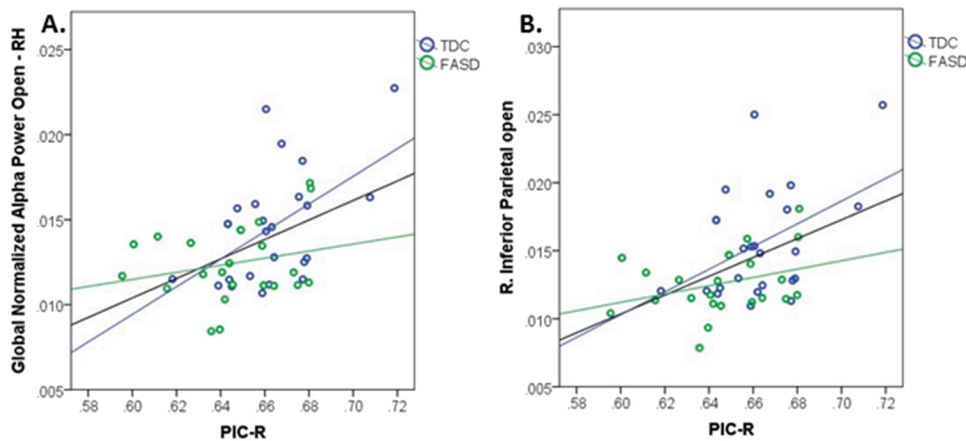


Fig. 3. A. Correlation between global normalized alpha power in the eyes open condition from right hemisphere (RH) and mean FA from right, posterior limb of the internal capsule (PIC-R). B. Correlation between right inferior parietal cortex normalized alpha power during eyes open condition vs. PIC-R. The overall sample regression line is shown in black, whereas the group regression lines are shown in blue (TDC) and green (FASD), respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Correlations between ROI mean FA and source-based alpha normalized power – r (corrected p-value) N.

All TDC FASD	PIC-R – Parietal RH	PIC-L – Parietal LH	AIC-L – Frontal LH
InfPar open	0.466 (0.013) 48 0.44 (ns) 25 0.325 (ns) 23	0.289 (ns) 49 -0.03 (ns) 25 0.379 (ns) 24	
InfPar closed	0.452 (0.015) 48 0.432 (ns) 25 0.376 (ns) 23	0.315 (0.038) 49 0.034 (ns) 25 0.478 (ns) 24	
SupPar open	0.338 (0.031) 48 0.286 (ns) 25 0.195 (ns) 23	0.298 (0.047) 49 -0.04 (ns) 25 0.399 (ns) 24	
SupPar closed	0.319 (0.038) 48 0.268 (ns) 25 0.237 (ns) 23	0.293 (ns) 49 0.012 (ns) 25 0.507 (ns) 24	
CaudAntCing open			0.318 (0.037) 49 0.231 (ns) 25 0.065 (ns) 24
CaudAntCing closed			0.285 (ns) 49 0.161 (ns) 25 0.207 (ns) 24
SupFront open			0.441 (0.011) 49 0.466 (ns) 25 0.097 (ns) 24
SupFront closed			0.391 (0.016) 49 0.371 (ns) 25 0.203 (ns) 24
Precentral open	0.412 (0.013) 49 0.425 (ns) 25 0.117 (ns) 24	0.478 (0.031) 49 0.27 (ns) 25 0.542 (ns) 24	
Precentral closed	0.401 (0.014) 48 0.416 (ns) 25 0.261 (ns) 23	0.431 (0.012) 49 0.271 (ns) 25 0.517 (ns) 24	

generation. These consistent results indicate that normalized alpha power provides sufficient signal to noise to examine multimodal associations with FA regardless of state (eyes-open vs. -closed) and may reduce participant burden in future studies.

Resting alpha oscillations have most frequently been examined in parietal/occipital cortex based on the association with occipital alpha oscillations (Clayton et al., 2018). Here we found significant correlations between anterior limb of the internal capsule and frontal alpha power and the posterior limb of the internal capsule and sensorimotor cortex suggesting that resting alpha oscillations are driven by the thalamus throughout the cortex. That is, mean FA is consistently associated with normalized alpha power. One possible explanation for this lack of regional specificity is that the MEG measures may blur signal spatially. The minimum norm source analysis approach used tends to spread signal spatially (Hauk et al., 2011), however, this does not explain the

consistency of the results at the sensor level. The sensor level analysis was performed using only the planar gradiometers and these are only sensitive to activity in the near vicinity of the sensors and sensors over parietal cortex are unlikely to detect activity from frontal cortex under normal physiological conditions (Hamalainen et al., 1993). A similar argument can be made for the source level correlations. While a minimum norm estimate will cause some signal leakage often beyond the extent of the original generator, the source spread often remains within the size of a cortical lobe and does not extend from parietal to frontal sources (Hauk et al., 2011). Therefore, we interpret the results as indicating that thalamocortical tracts are broadly impacted by PAE and these each influence alpha power within their corresponding lobe.

Despite the strengths of the study, limitations remain. First, the lack of significant correlations within individual groups is likely related to the small sample size. However, the results overall are consistent with a linear relationship between mean FA in corticothalamic tracts and alpha power. Future studies would benefit from larger sample sizes to account for variability in uncontrolled factors. Second, it is important for future studies to examine if the amount of alcohol consumed or the pattern of prenatal alcohol exposure influenced this relationship. Third, the study results would be stronger if both groups were matched on SES. In this case, SES was not significantly associated with FA but future samples would benefit from a more closely matched sample based on the finding that attention abilities are often reported to be lower in children from lower SES households (St John et al., 2019). Fourth, prior studies (Paolozza et al., 2015, 2017) indicate that white matter deficits may be influenced by age and sex. Due to the small sample size, the well-matched age/sex distribution, and the relatively narrow age-range, we did not examine age as a covariate or examine differences in developmental patterns by sex. Fifth, the results represent a correlation from a cross-sectional sample. A longitudinal sample will provide stronger evidence for the relationship between FA and alpha power and its role in mediating attention in children.

In conclusion, the current study demonstrates group differences in corticothalamic connectivity in children with and without an FASD and that this connectivity was correlated with resting alpha power. These results provide additional evidence for the underlying mechanisms that lead to altered behavior in children with an FASD. Future studies will need to examine if resting alpha oscillations impact attention abilities in children as assessed with neuropsychological measures and determine if interventions can alleviate these deficits.

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.

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Research Data

The data for this study will be made available upon request to the corresponding author through the COINS data exchange.

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