

Quantitative assessment of cerebral connectivity deficiency and cognitive impairment in children with prenatal alcohol exposure ^F

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ABSTRACT

It is common knowledge that alcohol consumption during pregnancy would cause cognitive impairment in children. However, recent works suggested that the risk of drinking during pregnancy may have been exaggerated. It is critical to determine whether and up to which amount the consumption of alcohol will affect the cognitive development of children. We evaluate time-varying functional connectivity using magnetoencephalogram data from somatosensory evoked response experiments for 19 teenage subjects with prenatal alcohol exposure and 21 healthy control teenage subjects using a new time-varying connectivity approach, combining renormalised partial directed coherence with state space modeling. Children exposed to alcohol prenatally are at risk of developing a Fetal Alcohol Spectrum Disorder (FASD) characterized by cerebral connectivity deficiency and impaired cognitive abilities. Through a comparison study of teenage subjects exposed to alcohol prenatally with healthy control subjects, we establish that the inter-hemispheric connectivity is deficient for the former, which may lead to disruption in the cortical inter-hemispheric connectivity and deficits in higher order cognitive functions as measured by an IQ test, for example. We provide quantitative evidence that the disruption is correlated with cognitive deficits. These findings could lead to a novel, highly sensitive biomarker for FASD and support a recommendation of no safe amount of alcohol consumption during pregnancy.

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Fetal alcohol spectrum disorders (FASDs), characterised by impaired cognitive abilities, are a group of conditions that can occur in a person whose mother has consumed alcohol during pregnancy. Surveys from the United States have found that about 10% of pregnant women have consumed alcohol in the last month and 20% to 30% at some point during the course of the pregnancy.

Although there is clear evidence that children exposed to alcohol prenatally are at risk of developing an FASD, some studies have argued that the risk of problems depends on the amount consumed, the frequency of consumption, or when during pregnancy the alcohol was consumed. Our study involving experimental data collected from teenage subjects, combined with mathematical

modeling, shows that there is no safe amount or safe stages during pregnancy for alcohol consumption. We employ a new time-varying connectivity approach to estimate the fast changing information flow among the brain sources using magnetoencephalogram data of somatosensory evoked response experiments from 19 teenage subjects with prenatal alcohol exposure (PAE) and 21 healthy control (HC) teenage subjects. We demonstrate that the inter-hemispheric connectivity is deficient for subjects with prenatal alcohol exposure. A lack of the inter-hemispheric connectivity is known to facilitate autism, stroke, schizophrenia, as well as dementia, disrupts the cognitive performance, and may lead to neurobehavioral deficits. We show that the disruption in the inter-hemispheric connectivity observed in this study is correlated with cognitive deficits associated with FASD, suggesting a potential new biomarker for FASD. Based on our findings, we support the recommendation of no safe amount of alcohol during pregnancy.

I. INTRODUCTION

Fetal Alcohol Spectrum Disorder (FASD, American Academy of Pediatrics, 2000) is recognized as one of the leading causes of intellectual disability, resulting in significant cognitive deficits in 2%-5% of children^{1,2} with no associated genetic origin.³ A recent study conducted in the United States of America reports that 10.2% of pregnant women are drinking alcohol,⁴ compared with 63.6% of non-pregnant women in childbearing age. With a typical delay of 4 weeks in recognizing pregnancy,⁵ a majority of women likely continue drinking and exposing their foetus to alcohol at least in the early stages of their pregnancy.⁴ Despite recent claims that the risk of drinking during pregnancy is exaggerated,^{6,7} a meta-analysis of 34 cohort studies demonstrates a significant detrimental association between binge prenatal alcohol exposure and child cognition.⁸ This is supported by advanced brain imaging studies that reveal structural, metabolic, and functional brain abnormalities associated with prenatal alcohol exposure.^{9,10} For mild-to-moderate prenatal alcohol exposure, a positive but small association with child cognition was found in a large study but with limited access to detailed outcome measures.⁸ Despite extensive preclinical studies examining the mechanisms underlying prenatal alcohol effects, there is little information about how drinking during pregnancy affects brain development in children. Only a few studies systematically examined the connectivity of the corresponding brain networks during the resting state¹¹⁻¹³ and working memory tasks in FASD children.¹⁴ The lack of studies investigating this type of connectivity can in part be attributed to a lack of methodology capable of reliably revealing the functional connectivity from data. Recently, a method was proposed and validated through an overarching framework for data-based modeling.^{15,16} Applying this overarching framework to magnetoencephalographic (MEG) measurements after reconstructing their sources in the brain enables us to analyze the location and timing of electrophysiological deficits associated with prenatal alcohol exposure with unprecedented precision,^{15,16} offering a quantitative evaluation of the alterations to the developing brain when exposed prenatally to alcohol and its cognitive deficits.

In this paper, we hypothesize that alcohol exposure during pregnancy, even a mild or moderate amount, does result in cortical

inter-hemispheric connectivity deficiency and does cause cognitive impairment in children, and validate it through a comprehensive and multitude data analysis. We provide, for the first time, a quantitative characterization of the hypothesis. Specifically, we conducted an observational cohort study and collected somatosensory evoked MEG response time series from 21 healthy control teenage subjects (HC group: 12 males, 9 females; age: 15.2 ± 2.6 yr) and 19 subjects with prenatal alcohol exposure (PAE group: 13 males, 6 females; age: 16.4 ± 2.1 yr), with no significant difference in age and gender between the HC group and the PAE group (unpaired t-test for age: $P \approx 0.201$ and $t \approx 1.304$; χ^2 test for gender: $\chi^2 \approx 0.007$, $P \approx 0.935$). We applied the overarching framework to reveal the time-dependent change in inter-hemispheric functional connectivity and consequently the corresponding information flow if not absent during somatosensory evoked response for children with moderate or consistent prenatal alcohol exposure and to explore the correlation between inter-hemispheric functional connectivity and cognitive performance quantitatively. Our study will clear up the recent controversy on a significant matter that has long lasting impacts on public health and the well-being of the society.

II. METHODS AND MATERIALS

A. Experimental design and procedure

The experimental protocols were approved by the Human Research Review Committee at the University of New Mexico Health Sciences Center, Albuquerque, NM. The ethical approval/informed consent was obtained to use the data for the analyses. The human somatosensory evoked MEG responses were collected as a part of a separate study. Prior to the study, each subject provided written informed consent. MEG data from 21 healthy teenage subjects (12 males, 9 females; 15.2 ± 2.6 yr old, age \pm SD) and 19 subjects with prenatal alcohol exposure (13 males, 6 females; 16.4 ± 2.1 yr old, age \pm SD) were collected in a magnetically shielded room (Vacuum-schmelze—Ak3B) at the Mind Research Network in Albuquerque, using a 306-channel whole-head MEG system (Elekta Neuromag) at a sampling rate of 1000 Hz and a bandpass filter between 0.1 Hz and 330 Hz to avoid drifts and aliasing. Prior to the experiment, fiducial points (left and right preauricular points and nasion) and head shape data were collected and checked by the Polaris system. Participants sat upright during the task and were monitored at all times by an audio and video link between the magnetically shielded room and the control room. The 306-sensor MEG system measured the magnetic field distribution around the whole head of the seated subjects. The system was fully equipped with real-time motion correction and artifact rejection software. Movement was corrected to the initial head location using the movement correction algorithm provided with the Neuromag software package. These motion corrected data sets were further analyzed in our study without concern of the movement of subjects across epochs. Subjects were quietly sitting with their head positioned inside the MEG helmet while stimuli were presented. Somatosensory stimuli were generated by allowing a short pulse of compressed air to fill an air bladder that was attached to the subjects' right index finger. The air pulse was controlled by the Presentation software and a compressed air regulator (located outside the shielded room). The air puff stimulus lasted 50 ms with an ISI of 1.0-1.4 s. The air bladder pressure applied to the index finger

was monitored and recorded simultaneously with MEG collection for offline analysis and interpretation of the results. We collected 120 to 180 trials for the right index finger of each subject.

The 60 Hz power line noise was removed.¹⁷ Raw MEG data were filtered for noise sources such as eye blinks and excessive movement and then corrected for head motion using the Neuromag MaxFilter software.¹⁸ Heartbeat artifacts were removed by projecting electrocardiogram (ECG) data from MEG sensor waveforms using the signal-space projection (SSP) method.¹⁹ The data for each stimulus condition were obtained from 100 ms prior to the onset of the stimulus to 600 ms following stimulus onset. The data were baseline-corrected and subjected to a 50 Hz low-pass filter during signal processing.

Structural MRIs were obtained for use in mapping source locations from all the subjects. Sagittal T1-weighted anatomical MR images were collected using a Siemens TIM Trio 3 Tesla MRI system with a multiecho 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 mm × 256 mm, matrix = 256 × 256, 1 mm thick slice, 192 slices, GRAPPA acceleration factor = 2].

B. Brain connectivity analysis

Sources were localized for each subject using Cortical-Start Spatio-Temporal (CSST) multidipole analysis with integrated Multiple Signal Classification (MUSIC).²⁰ CSST source localisation was calculated based on the averaged responses occurring between 0 ms and 320 ms after the onset of the stimulus for responses to somatosensory stimuli. For each subject, the realistic cortical surface and three layers (inner skull, outer skull, and skin) were reconstructed from the anatomical MRI images using the Freesurfer software (Compumedics, Charlotte, NC). Following the selection of the optimal source model, the single-trial waveforms of each dipolar source were calculated within a realistic head model with the minimum norm estimate (MNE) software²¹ to yield the estimates of continuous time series of cortical currents. State space modeling was applied to the data and renormalized partial directed coherence (rPDC) values were estimated to measure the time-dependent effective connectivity (see eMethods and Table S1 in the [supplementary material](#)).

C. Statistical analysis

To test whether rPDC within the stimulation period is significantly different from a reference period for each group, rPDC is estimated for the somatosensory stimulation period (0 to 320 ms) and for a reference period prior to the stimulus (−100 to 0 ms). For the reference period, rPDC is averaged across time and frequency for each subject. The rPDC values for the somatosensory stimulation period are normalized by the reference rPDC values (−100 to 0 ms) for each subject. To compare the normalized rPDC values, i.e., the strength of the connections, between the two groups for the somatosensory stimulation period, the normalized rPDC values at each time-frequency point within a specified epoch, e.g., 0 to 320 ms, are extracted for comparison. To compare at the group level, for each group, the normalized rPDC is averaged across time, frequency, and subjects. The null hypothesis is that there is no difference between the normalized averages of the two populations.

III. RESULTS

A. Deficiency of late response

For the connectivity analysis applied to the MEG time series in response to somatosensory stimuli, we first reconstruct the sources using a three-dipole model for left primary somatosensory cortex (SI-l), right secondary somatosensory cortex (SII-r), and left secondary somatosensory cortex (SII-l), see Table S2 in the [supplementary material](#); the corresponding mathematical procedure is described in the eMethods in the [supplementary material](#). Figure 1(a) shows the average of somatosensory MEG waveforms with peaks at latencies of 71 ms and 201 ms for the HC group and at latencies of 73 ms and 97 ms for the PAE subjects. The average waveforms for both groups show an evoked response over the postcentral gyrus of the anterior parietal lobe, where primary and secondary somatosensory cortices (SI and SII) are located. The late somatosensory evoked MEG response around 200 ms appears deficient for the PAE subjects compared with the HC group [Fig. 1(b)]. Figure 1(c) shows the average time series of the estimated dipolar sources of the HC and PAE subjects. The spectral coherence between 5 Hz and 30 Hz averaged over frequency for all three possible connections is shown in Fig. 1(d) for the HC and PAE subjects. Coherence between SII-l and SII-r for the HC subjects is significantly higher than for the PAE subjects (Wilcoxon-test: $P \approx 0.007$, $t \approx 2.893$, see Table S3 in the [supplementary material](#)). This is predominantly the case between 10 Hz and 20 Hz [Fig. 1(e)]. To account for multiple testing, we Bonferroni-corrected the significance level rather than adjusting the P-value, and this correction for multiple testing was adopted throughout our work.

B. Impaired inter-hemispheric connectivity

PAE subjects were split into two groups based on the maternal drinking level (see Table S4 in the [supplementary material](#)): 13 subjects were consistently exposed to alcohol throughout the whole pregnancy (cPAE group), and 6 subjects were exposed to alcohol only occasionally (oPAE group). Among different groups, there is no significant difference in age (unpaired t -tests: HC vs oPAE: $P \approx 0.982$ and $t \approx 0.023$; HC vs cPAE: $P \approx 0.095$ and $t \approx 1.724$; oPAE vs cPAE: $P \approx 0.219$ and $t \approx 1.282$) or gender (χ^2 test: HC vs oPAE: $\chi^2 \approx 0.274$ and $P \approx 0.601$; HC vs cPAE: $\chi^2 \approx 0.189$ and $P \approx 0.664$; oPAE vs cPAE: $\chi^2 \approx 0.653$ and $P \approx 0.419$). Connectivity is analyzed using the overarching framework^{15,16} employing Granger causality inference by applying rPDC combined with state space modeling to the source time series of somatosensory evoked MEG. Figure 2(a) shows the time-frequency representation of rPDC, a split in time around 200 ms after stimulus is evident particularly in the HC group. Therefore, time-frequency regions from 0 ms to 200 ms and 201 ms to 320 ms, respectively, within a 5–30 Hz range that have significantly increased rPDC values compared with a reference interval, are used to generate functional connectivity graphs for the HC and PAE groups [Fig. 2(b)]. We consider a connection to be present whenever the average rPDC value divided by the average rPDC value of the reference period (−100 to 0 ms), i.e., the normalized average strength of a connection, is significantly higher than the one at a nominal significance level of 5% [Fig. 2(b)]. All three groups show connections from SI-l to both SII-l and SII-r during the early post stimulus epoch (0 to 200 ms). However, these two connections are considerably reduced if

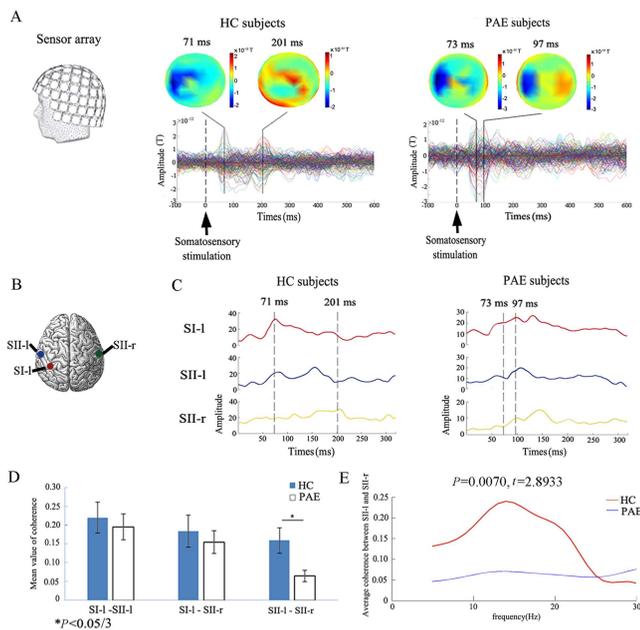


FIG. 1. Somatosensory evoked MEG data in sensor space and source space for HC and PAE subjects. (a) Sensor array showing the location of sensors. Group average waveforms and scalp topographies of MEG averages for HC and PAE groups. Time series of group average waveforms of each channel are superimposed in different colours. Scalp topographies are displayed at 71 and 201 ms for the HC group and at 73 and 97 ms for the PAE group. (b) Cortical sources localised using multi-dipole analysis: SI-I, SI-I-r, and SI-I-r. (c) Average source time series of somatosensory responses for MEG data from HC and PAE subjects. Vertical dashed lines indicate time points for which scalp topographies are displayed in (a). (d) Mean values of coherence between source locations for HC and PAE subjects; average coherence between SI-I and SI-I-r significantly higher in HC compared with PAE. (e) Spectral coherence between SI-I and SI-I-r averaged for HC (red) and PAE (blue) groups.

not absent for both the oPAE and the cPAE groups in the late post stimulus epoch (201 to 320 ms). The information flow from SI-I to SI-I during the early post stimulus epoch (0 to 200 ms), as well as the inter-hemispheric connection from SI-I to SI-I-r during the late post stimulus epoch (201 to 320 ms), is not statistically significant for either the oPAE or the cPAE group. For the oPAE group, an additional inter-hemispheric influence from SI-I-r to SI-I is found during the early post stimulus epoch (0 to 200 ms).

We further examined if the differences between the connections are statistically significant between the two groups (Table S5 in the [supplementary material](#)). We consider the same epochs of early post stimulus (0 to 200 ms) and late post stimulus (201 to 320 ms), as shown in [Fig. 2\(c\)](#). For the early post stimulus epoch, the normalized average strength of connection from SI-I to SI-I of the HC group is significantly larger (after Bonferroni correction) than that of the oPAE (unpaired *t*-test: $P < 0.0001$ and $t \approx 5.122$) and cPAE groups (unpaired *t*-test: $P < 0.0001$ and $t \approx 6.782$). For the late post stimulus epoch, the normalized average strength of connection from SI-I to SI-I-r (inter-hemispheric connectivity) of the HC group is significantly larger (after Bonferroni correction) than that of both the

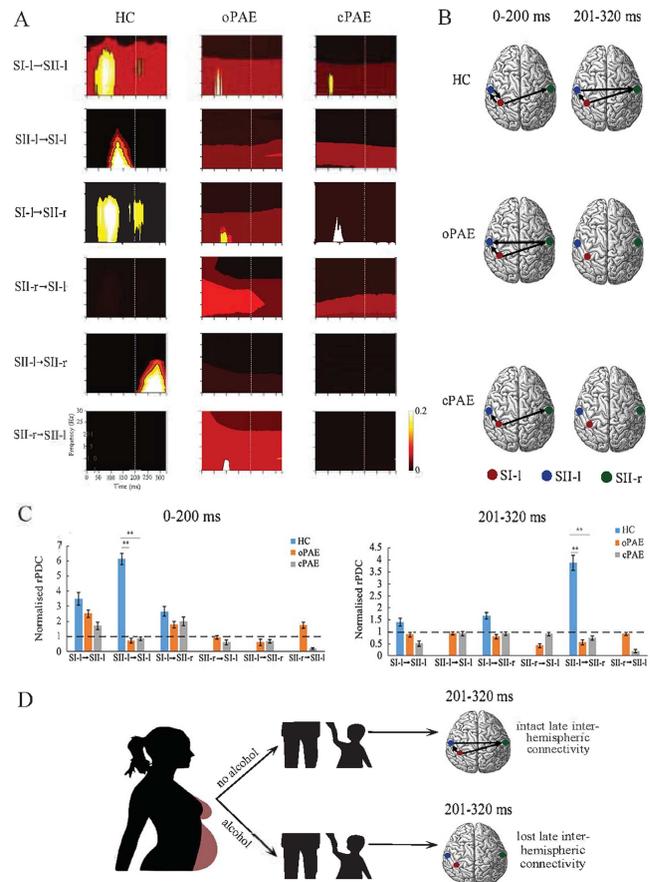


FIG. 2. Functional connectivity between SI-I, SI-I-r, and SI-I-r of the HC, oPAE, and cPAE groups. (a) Time-frequency representations of rPDC (colour coded) as a measure of causal influences within the neural network comprising SI-I, SI-I-r, and SI-I-r averaged across the HC, oPAE, and cPAE subjects. The bright colour (yellow/white) regions surrounded by black lines have significantly larger rPDC values than the mean rPDC in the reference interval prior to the stimulus (-100 to 0 ms) ($P < 0.01$, *t*-test with Bonferroni correction). The white dashed line in each plot indicates 200 ms; the x-axis (time, ms) and y-axis (frequency, Hz) are the same for all subplots. (b) Graphs obtained from rPDC analysis applied to source time series located at SI-I, SI-I-r, and SI-I-r for somatosensory evoked MEG of the HC, oPAE, and cPAE groups. Two different post stimulus epochs are considered. Arrows indicate connections for which the average rPDC values normalised by the reference rPDC value (-100 to 0 ms) are significantly higher than one (uncorrected alpha). (c) Average rPDC values normalised by the reference rPDC value (-100 to 0 ms) for somatosensory evoked MEG of the HC, oPAE, and cPAE subjects. Two different post stimulus epochs are considered, the early post stimulus epoch (0 to 200 ms) and the late post stimulus epoch (201 to 320 ms). The blue bars represent the HC group, the orange bars represent the oPAE group, and the gray bars represent the cPAE group. Significant differences of the strength of the connections between groups using a *t*-test with Bonferroni corrected significance level are highlighted by asterisks ($*P < 0.05/18$, $**P < 0.01/18$). (d) Schematic representation of the presented results. We compare somatosensory evoked MEG response time series of children with/without prenatal alcohol exposure. The reconstructed networks of the primary (red dot) and secondary (blue and green dots) somatosensory cortices show a lack of inter-hemispheric connectivity in the late response (201-320 ms after stimulus) for children prenatally exposed to alcohol.

TABLE I. Mean and standard error of the mean (SE) of cognitive measures for the HC, oPAE, and cPAE groups, respectively, and the *P*-value of unpaired *t*-tests for the cognitive measures between different groups.

Cognitive measures	IQ	SWM choice latency	CGT impulsivity index	IED stage 1 latency
HC group (mean \pm SE)	107.714 \pm 3.113 (n = 21)	809.90 \pm 39.33 (n = 21)	34.593 \pm 3.102 (n = 21)	2088.0 \pm 170.3 (n = 21)
oPAE group (mean \pm SE)	79.667 \pm 3.913 (n = 6)	898.55 \pm 93.56 (n = 5)	53.277 \pm 5.110 (n = 6)	3060.1 \pm 351.1 (n = 6)
cPAE group (mean \pm SE)	83.250 \pm 4.526 (n = 12)	1276.9 \pm 236.8 (n = 10)	51.844 \pm 5.209 (n = 11)	4837 \pm 1190 (n = 10)
HC vs. oPAE group (P-value)	<0.0001 ^a	0.3461	0.0076	0.0142
HC vs. cPAE group (P-value)	<0.0001 ^a	0.0103	0.0050	0.0470
oPAE vs. cPAE group (P-value)	0.5581	0.2955	0.8610	0.1813

^a*P* < 0.01/12.

oPAE (unpaired *t*-test: *P* < 0.0001, *t* \approx 6.222) and the cPAE groups (unpaired *t*-test: *P* < 0.0001, *t* \approx 10.588). These differences in the inter-hemispheric connectivity between the HC and the PAE groups from SII-l to SII-r are consistent with the results of average coherence as shown in Fig. 1(d). Thus, the inter-hemispheric functional connectivity is dramatically reduced during somatosensory evoked response for children with moderate or consistent prenatal alcohol exposure, as shown in Fig. 2(d).

C. Relation to cognitive performance

To characterize the cognitive performance of the subjects quantitatively, we used an IQ test, Cambridge gambling task (CGT), spatial working memory task (SWM), and intra-extra dimensional shift task (IED) (see Tables S6 and S7 in the [supplementary material](#)). In particular, on the same day before the MEG experiment, all the subjects performed the tests for the first time. We compare the cognitive measures for the HC and PAE groups using unpaired *t*-tests as shown in Table I, where the *p*-values are considered significant if *P* < 0.05/12 (Bonferroni correction). The results show a significantly lower IQ in both the oPAE and the cPAE groups in comparison with the HC group, indicating a significant level of impairment in the cognitive and behavioral domains in adolescents with PAE. No significant differences were found between the cPAE and the oPAE subjects for the IQ test and neither for the other tests after correction for multiple testing.

We investigate the quantitative relationship between the late inter-hemispheric connectivity strength from SII-l to SII-r and cognitive performance of the subjects using the Spearman correlation between the rPDC values (SII-l to SII-r, 201 to 320 ms) for each group and the cognitive measures. The results are shown in Table II. There are significant correlations between the rPDC values from SII-l to SII-r and IQ (*r* \approx 0.605 and *P* < 0.0001) after Bonferroni correction, CGT impulsivity index (*r* \approx -0.461 and *P* \approx 0.004), and the latency of IED shift task (*r* \approx -0.828 and *P* < 0.0001), as shown in Fig. S1 in the [supplementary material](#). While the effect of IQ could straightforwardly be explained by the difference in IQ performance as well as the difference in inter-hemispheric connectivity, the association for CGT and IED is somewhat unexpected. Of particular interest is whether or not the correlations remain in the subgroups. Our analysis reveals a significant association between the rPDC values from SII-l to SII-r and the latency of IED shift task for HC (*r* \approx -0.865 and *P* < 0.0001)

subjects after Bonferroni correction. The Pearson correlation analysis results are shown in Table S8 in the [supplementary material](#).

IV. DISCUSSION

It is common wisdom that pregnant women should not drink alcohol. However, this well known notion was recently challenged.^{6,7} Is it really true that moderate prenatal exposure to alcohol will have little effect both on the connectivity and on the cognitive ability of children? Our comprehensive and quantitative study provides a negative answer. In particular, we analyze MEG recordings from somatosensory evoked responses in children prenatally exposed to alcohol and healthy control subjects and investigate the association between connectivity strengths of the inter-hemispheric coupling and measures of the cognitive performance in those young adults. The study is necessarily an observational cohort study limiting the possible causal inference that can be drawn from it. Apparent latent confounders such as gender or age were ruled out as explanatory factors. The late latency component of the somatosensory evoked response after 200 ms is lower if not absent for PAE subjects. A time-varying functional connectivity analysis reveals that, statistically, the

TABLE II. Spearman correlation analysis between the rPDC values (201 to 320 ms, SII-l to SII-r) and the cognitive measures for the pooled subjects (HC and PAE), HC, and PAE groups, respectively.

Cognitive measures	Group	<i>r</i>	<i>P</i>
IQ	HC and PAE	0.6053	<0.0001 ^a
	HC	-0.0507	0.8273
	PAE	0.2190	0.3826
SWM choice latency	HC and PAE	-0.2782	0.1004
	HC	-0.0130	0.9573
	PAE	0.1429	0.6114
CGT impulsivity index	HC and PAE	-0.4612	0.0039 ^b
	HC	-0.1013	0.6614
	PAE	0.1618	0.5339
IED stage 1 latency	HC and PAE	-0.8276	<0.0001 ^a
	HC	-0.8649	<0.0001 ^a
	PAE	-0.6618	0.0065

^a*P* < 0.01/8.

^b*P* < 0.05/8.

inter-hemispheric cortical information flow from SII-l to SII-r at late latencies after 200 ms is reduced in the PAE subjects when compared with that in the HC subjects.

The corpus callosum is the major neural pathway connecting homologous cortical areas of the two cerebral hemispheres, which serves to communicate an inhibitory or excitatory influence on the contralateral hemisphere.^{22,23} There is a clear correspondence between cognitive function and inter-hemispheric connectivity as evidenced by patients who undergo callosotomy to treat epilepsy.²⁴ Previous works demonstrated underlying abnormalities in the microstructure of corpus callosum fibers for FASD subjects, especially in the posterior regions.^{25–28} This is consistent with our results of impaired inter-hemispheric connectivity for FASD subjects. An association between cognitive dysfunction and reduced inter-hemispheric connectivity has been reported in schizophrenia^{29,30} and multiple sclerosis^{31,32} with sensory processing abnormalities, as well as autism,³³ depression,³⁴ and Alzheimer's disease³⁵ with unresponsiveness, both being symptoms of FASD. It remains to be determined if the reduced inter-hemispheric connectivity is a result of these conditions or involved in their development.

Our results of the relationship between the late inter-hemispheric connectivity strength and the cognitive performance indicate that both moderate and consistent drinking during pregnancy affect the cortical connectivity and, by extension, the higher cognitive functions of children. With our measure of the inter-hemispheric rPDC values, a separation of the PAE and the HC subjects is possible. We can even show a clear association between the inter-hemispheric connection strength and the intra-extra dimensional shift task (IED) within the HC group. As apparent explanatory factors have been ruled out, we speculate that there is an immediate causal link between the weakening of the inter-hemispheric connection strength and the cognitive performance as measured in the IED task, which offers a differentiated assessment of shifting from previously reinforced stimuli and features. While the IED task does not explicitly test inter-hemispheric connectivity, it is a complex executive function task which likely requires coordination between the two hemispheres. The measure obtained here indicates impaired inter-hemispheric connectivity that also contributes to the cognitive difficulties experienced by children with PAE. Our findings could lead to a new biomarker for FASD, providing a highly sensitive, more objective criterion rather than trainable IQ tests. Our results imply that, to protect children from cognitive impairment, prenatal alcohol exposure should be avoided altogether.

V. CONCLUSION

The common sense advice “Please do not drink alcohol during pregnancy!” still applies, but it is now validated and backed up by our work that shows that prenatal alcohol exposure can lead to both deficiency in cortical inter-hemispheric connectivity and cognitive impairment occurring from both occasional and consistent drinking. Furthermore, our study reveals quantitatively a strong correlation between inter-hemispheric functional connectivity and cognitive performance for healthy control and prenatal alcohol exposure subjects. This work presents major evidence that children exposed

to alcohol prenatally are at risk of suffering from impaired cognitive abilities and other secondary factors, providing the recommendation of no safe amount of alcohol consumption during pregnancy.

SUPPLEMENTARY MATERIAL

See the [supplementary material](#) for the complete results and the details of the methods.

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