Original Article

Functional Language Network Connectivity in Children of Women with Epilepsy with Selective Antenatal Antiepileptic Drug Exposure

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Abstract

Purpose: Children of women with epilepsy and antenatal antiepileptic drug (AED) exposure have increased risk of language dysfunction. Our objective was to compare language related functional MRI network connectivity (FC) of children with women with epilepsy with antenatal AED exposure (CAED) with that of healthy children (COAED) for delineating functional basis of the language dysfunction. **Methods:** CAED under prospective follow up in Kerala Registry of Epilepsy and Pregnancy were consecutively sampled. COAED were identified from volunteers with normal brain MRI. Clinical Evaluation of Language Fundamentals score (CELF) was used to assess language. Functional MRI done using verb generation paradigm to activate language areas and key language network nodes were identified. A multivariate ROI-to-ROI and Seed-to-Voxel based FC was done using the selected seed regions in the language areas located in the right and left hemisphere in all subjects using the CONN functional connectivity toolbox in SPM8 under MATLAB. **Results:** Strong connectivity was observed within the identified language network between all language nodes bilaterally in CAED compare to controls. The mean connectivity strength of language network (LN) on the left side in CAED was 9.63 ± 4.62 (Mean ± SD) while for COAED it was 6.96 ± 3.67 (p=0.0001). The mean connectivity strength of LN between CAED (4.86 ± 1.07) and COAED (4.32 ±1.2) on the right hemisphere was not statistically significant (p=0.18). **Conclusion:** CAED with impaired language function had significantly increased functional connectivity which may indicate poor differentiation and localization of language centers.

Keywords: Antiepileptic drugs, children of women with epilepsy, functional connectivity, functional MRI, language network

Introduction

Children with antenatal exposure to antiepileptic drugs (AEDs) are at risk of lower cognitive functions than healthy children.[1-4] Neuropsychological studies in children with antenatal AED exposure have demonstrated varying levels of impairments in intelligence, memory, attention, and language. Our previous study had shown that the WISC score for children with antenatal AED exposure (n = 190) was 8.5 points lower than that of children without any AED exposure in the antenatal period.[5] They experience difficulties with expressive language, word comprehension, and repetitive language skills. The exact pathophysiological mechanism underlying these deficits were largely unclear though several factors like socioeconomic, genetic, environmental, and maternal factors were implicated. The VBM analysis had shown reduced total and gray matter volumes in children of women with epilepsy (CWE).[6]

Nevertheless, their cerebral functional imaging characteristics have not been examined. Functional network connectivity (FC) displays the temporal association between different regions of interest (ROI) in the brain. In the resting state, a robust FC connectivity between two or more ROIs indicates the simultaneous activation of those ROIs. However, it does not necessarily mean that those ROIs are anatomically connected in a network. In seed to voxel analysis, the connectivity between different ROIs in response to a language stimulus is examined.

We aimed to characterize the FMRI and Functional network connectivity (FC) concerning the language function in children of women with epilepsy with exposure to AEDs in the antenatal period (CAED). We compared the FC characteristics between a group of CAED and a group of age and sex-matched healthy children without any exposure to AEDs in their antenatal period (COAED). Both the ROI to ROI and Seed-to-Voxel analysis were performed for the two groups, CAED and COAED.

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Materials and Methods

Study design

This study was carried out in the Kerala Registry of Epilepsy and Pregnancy (KREP). The KREP is a registry that follows up women with epilepsy from the preconception period through pregnancy and delivery. The details of the registry and its protocol were published elsewhere.[4] All children under KREP are followed-up prospectively with EEG and tests for language and intelligence, at 12 months, twice between 6 years, and 12 years of age. We invited all the children living in two nearby districts who fulfilled the selection criteria. The selection criteria were: Age between 8 and 12 years, fluent in local language Malayalam, and residence within 50 km from the study center. They should have given their assent and informed consent (from guardians) and completed the neuropsychological and language examinations within 2 months of the MRI examination. The details of maternal epilepsy, antenatal AED exposure, birth, and development of the CAED were extracted from clinical records of registry.

Age and sex-matched children of similar socioeconomic status without antenatal exposure to AED formed the controls (COAED). The COAED were selected from volunteers, hospital visitors, and children attending to hospital for minor ailments. Exclusion criteria for both CAED and COAED included a history of maternal use of alcohol, tobacco, and other drugs during pregnancy and heritable disorders like tuberous sclerosis. Children with epilepsy, severe mental retardation, history of birth asphyxia, history of any acquired neurological insult, congenital malformation, or metallic implants were also excluded from the study. Children with normal vision, hearing, neurological examination, and normal structural MRI were only included in the study.

An expert neuropsychologist (KMA) and a speech pathologist (AN) administered the standardized battery of clinical neuropsychological and language tests to the CAED and COAED. The intelligence test was done using a Malayalam translation of the Wechsler Intelligence Scale for Children (WISC-IV). We used the normative data on this translation that was generated earlier by administering to a large number of school-going children.[5] We used a Malayalam translation of the Clinical Evaluation of Language Fundamentals (CELF) 4th Edition (Pearson) for which we had generated normative data earlier. The chief components of language assessed under CELF IV were Core Language Standard Score (CLSS), Receptive Language Standard Score (RLSS), Expressive Language Standard Score (ELSS), and Language Content Standard Score (LCSS).

Magnetic resonance imaging protocol and analysis

The MR imaging was performed on a 1.5 Tesla Magnetic Resonance scanner (Avanto SQ engine, Siemens, Erlangen, Germany). For precise anatomical evaluation, a 3-D FLASH sequence (Fast Low Angle Shot), which is a high-resolution 3D T1 weighted images of the brain, was obtained (TR/TE 11/4.94 ms, flip angle 15°, FOV 256 mm, slice thickness 1 mm and matrix of 256 × 256). A 3-D FLAIR (Fluid Attenuated Inversion Recovery) sequences with TR/TE/TI 5,000/405/1, 800 ms, FOV 256 mm, slice thickness 1 mm, matrix 256 × 256 were acquired in axial plane to evaluate the presence of any cortical or white matter lesion. Whole-brain functional images were acquired using T2* Echo planar imaging sequences sensitive to BOLD signal with TR-3580; TE-30; matrix = 64 × 64; FOV 256; the number of slices-36; with slice thickness 3 mm and 0 mm gap. The head was immobilized using soft pads placed around the head. All children were given proper training before the actual procedure for reducing movement artifacts.

MRI paradigm

All the subjects were given an appropriate description and rehearsal of the procedure and the paradigm before the tests. One visual language fMRI paradigm—visual verb generation (VVG), was presented visually to stimulate language areas. Here, a stimulus was presented visually through a small MR compatible screen in front of the participants and the screen was connected to MRI console. The pictures of nouns were shown and the child was asked to silently generate the corresponding verb of the noun shown on the screen. The pictures of cross wires were shown during the rest phase [Figure 1]. It was a block design paradigm consisting of alternating blocks of 5 active and 5 rest conditions, each block consisting of 10 measurements and lasting for 30 s. The total acquisition time was 6 min. There were 100 measurements per session.

Image data acquisition

FMRI data analysis was done using SPM8–Statistical Parametric Mapping software (Wellcome Department of Imaging Neuroscience, University College. London. www.fil.ion.ucl.ac.uk/spm) which works with MATLAB version 7.7 0.471. The functional images were initially on and realigned, then co-registered to high-resolution structural T1Weighted image—T1MPR and normalized to MNI template (Montreal Neurological Institute) provided in the SPM 8 toolbox. After normalization, the images were smoothened with 8 × 8 × 8 mm^3 FWHM Gaussian filter. The paradigm was a block design paradigm with 5 active and 5 rest conditions. Each block consists of 10 measurements and lasted for 30 seconds. This was incorporated in the design matrix with other regressors like movement and a filter cut off of 128 seconds. The total acquisition time was 6 min for each paradigm. Single participants'data were evaluated for the BOLD response, and a statistically significant difference in activation between rest and active phases was computed for both COAED and CAED using a GLM. We also evaluated group differences between COAED and CAED using a z statistical threshold of 2.7 and a cluster threshold of 50. From this, we identified language areas with significantly activated voxels ($P < 0.05$) in each hemisphere for group differences.

Functional connectivity analysis

It was performed using the active phase of the VVG using the CONN functional connectivity toolbox (Whitefield and

Nieto-Castanon, 2012, version 16p http://web.mit.edu/swg/software.htm) in SPM8 under MATLAB.

Preprocessing and ROI selection

We selected 6 ROIs in the language areas on either cerebral hemisphere [Table 1] which showed significant activation during verb generation task (corrected $P < 0.05$). ROI selections were based on task-based activation, which is a reliable method for assessing functional connectivity.[7] Preprocessing for connectivity analysis included spatial realignment, slice timing correction, normalization to MNI EPI template, co-registration to structure, and smoothing. After preprocessing all potential confounding variables like 3D motion parameters, noise secondary to white matter and cerebrospinal fluid signals were added as regressors based on Comp-Cor method analysis.[8] No global signal regression was applied. A temporal filter of 0.008 and 0.08 Hz was applied to remove low-frequency fluctuation waves. ROI to ROI and Seed-to-Voxel based connectivity analysis was performed for the task condition. Average BOLD signals from the selected ROIs for each subject in CAED and COAED group were extracted. A multivariate ROI-to-ROI correlation approach was used to assess FC for the seed regions located in the right and left hemispheres in the selected language areas. Group level connectivity maps were obtained at a statistical threshold of $P < 0.05$, FDR corrected. The connectivity network was converted to a normal distribution using Fisher's z transform and the signal was averaged across subjects to produce a single average correlation measurement.

We applied independent sample *t*-test to compare continuous variables and Chi-square test to compare proportions. Correlations between the neuropsychological tests, language tests, and the FC results were carried out with logistic regression.

Results

Subject characteristics

FMRI scanning was done in 35 CAED and 19 COAED children. We excluded 4 CAED subjects (3 for incomplete neuropsychological tests and 1 for movement artefact). Final FMRI analysis was done on 31 CAED and 19 COAED. The demographic and language data for both CAED and COAED were given in Table 2. There were 11 males (8 females) in COAED and 22 males (9 females) in CAED group. The mean age of CAED was 10.52 ± 1.05 years and for COAED was 10.58 ± 0.961 years. The age ($P = 0.822$) and sex ($P = 0.23$) were not statistically significant.

Mothers of CAED were taking AEDs during pregnancy (74% on monotherapy and 26% on polytherapy). The AEDs used as monotherapy (or polytherapy) were carbamazepine 5 (8), phenobarbitone 6 (6), valproate 10 (4), phenytoin 2 (0), and diazepam1 (0). The seizure frequencies during the entire pregnancy period for the CAED group were no seizures for 43%, 1–3 seizures for 25%, and more than 3 for 32%. Maternal seizures were generalized-tonic-clonic type for 18, focal with impaired awareness for 12, and focal with awareness for 1.

Table 1: Seed Regions for language FC for CAED and COAED group

Region	Broadman's Area	Peak MNI Coordinates		
		X	y	Z
Right Hemisphere				
ITG	BA-45	49.7	26.56	4.42
IOG	BA-44	51.09	11.06	19.5
MFG	BA-6	42.01	48.52	18.40
P-STG	BA-22	65.29	-48.33	19.94
SMG	BA-40	64.11	-50.94	25.13
AG	BA-39	57	42.1	18
Left Hemisphere				
ITG	BA-45	-48	9.77	19.8
IOG	BA-44	57.5	17.52	5.7
MFG	BA-6	-42.01	48.52	18.40
P-STG	BA-22	-64	-52.23	19.94
SMG	BA-40	-64.11	-49.65	25.23
AG	BA-39	-58.0	-43.1	18.01

ITG, Inferior Triangular Gyrus; IOG, Inferior Frontal Gyrus; MFG, Middle Frontal Gyrus; P-STG, Posterior Superior Temporal Gyrus; SMG, Supra Marginal Gyrus; AG, Angular Gyrus

Table 2: Comparison of age, sex, language test, and FSIQ of CAED and COAED

	CAED	COAED	Group effect-*P*
Age-Mean±SD	10.64±1.05	10.50±0.99	0.622
Sex-M/F*	24/7	11/8	0.878*
MLT			
CLSS Score	79.16±20.9	90.18+15.82	**<0.02**
LCSS Score	88.62±17.44	98.18+18.66	**<0.04**
ELSS Score	83.0±21.29	90.10+18.15	0.178
RLSS Score	82.96±24.11	89.22+15.00	0.272
FSIQ	78.96±14.62	87±13.5	**<0.005**

MLT, Malayam Language test; CLSS, Core Language Standard Score; LCSS, Language Content Standard Score; ELSS, Expressive Language Standard Score; RLSS, Read Language Standard Score; FSIQ, Full Scale IQ. *Chi-square Test. Bold value indicate the significance level was set at *P* value<0.05

The syndromic classification of their epilepsy was generalized epilepsy for 10, juvenile myoclonic epilepsy for 12, and focal epilepsy for 14 women. With regard to the type of epilepsy, 10 had generalized epilepsy, 12 had GE-Juvenile myoclonic epilepsy, and 14 had focal epilepsy. The maternal IQ was a mean IQ of 80.5 ± 11.31.

Intelligence and language test

The mean Full-Scale IQ (FSIQ) for the CAED was 78.96 ± 14.62 (range 52–110) and for the COAED was 87.0 ± 13.5. The FSIQ of the CAED group was 8 points lower than that of COAED group which was statistically significant ($P < 0.005$). The core language standard score (CLSS) for the CAED was 79.16 ± 17.82 and the COAED was 90.18 + 15.82. The mean CLSS score for the CAED group was 9.76 points less than the COAED group and was statistically significant ($P < 0.02$). The language content standard score (LCSS) for the CAED was

88.62 ± 17.44 and the COAED was 98.18 ± 18.66 and was statistically significant ($P < 0.04$). Though the mean expressive language standard score (ELSS) and read language standard score (RLSS) was less for CAED compared to COAED, it was not statistically significant ($P = 0.178$ and 0.272, respectively).

Functional connectivity results

The ROI-to-ROI connectivity analysis revealed that CAED had a widespread increase in functional network connectivity related to language nodes involving both frontal and temporoparietal regions compared to COAED [Figures 2 and 3]. The seed-to-voxel based FC also showed an increased FC network of language areas over frontal and temporal regions [Figure 4]. The FC strength for language network (LN) was significantly increased on the left cerebral hemisphere in CAED compared to COAED group (P-value <0.002). The mean connectivity strength of the language network on the left side in CAED was 5.63 ± 2 (Mean ± SD) while for COAED it was 3.67 ± 1.31. The mean connectivity strength of LN between CAED (4.86 ± 1.07) and COAED (4.32 ± 1.2) on the right hemisphere was not statistically significant ($P = 0.18$).

Figure 1: Visual verb generation paradigm with active phase showing pictures of noun and rest phase showing cross wires

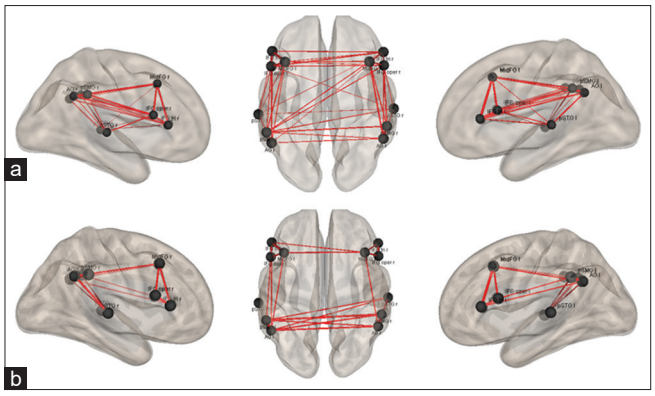

Figure 3: FC results overlaid in a 3D brain view in sagittal (left and right) and axial sections (middle). There is an increased functional connectivity network for language areas in CAED (a) compared to COAED (b)

The language nodes in CAED had higher interhemispheric connectivity and intrahemispheric connectivity. The highest interhemispheric FC in CAED was between left MFG and right ITG (T value 5.52, $P < 0.00001$) and the highest intrahemispheric FC was between left ITG and left MFG (T value 9.96, $P < 0.00001$). In COAED, the maximum interhemispheric FC was between right and left PSMG (T value 4.41, $P < 0.04$). Their maximum intrahemispheric FC was between left AG and left PSMG (T value 6.94, $P < 0.00092$) and also between right AG and right PSMG (T value 6.94, $P < 0.000935$).

Correlation between language function and connectivity scores

A positive trend was seen between FC z score and CL_SS (r2 = 0.018, $P = 0.517$), RL_SS (r2 = 0.003, $P = 0.807$), EL_SS (r2 = 0.127, $P = 0.080$), LC_SS (r2 = 0.019, $P = 0.510$), although it was not statistically significant [Figure 5].

Discussion

The background of a long-standing registry of epilepsy and pregnancy offered us the opportunity to study the fMRI and FC language network in a well-characterized cohort of

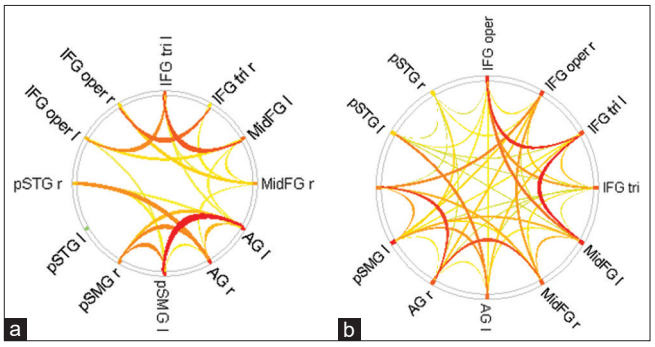

Figure 2: FC Analysis (Connectome ring) of language areas between COAED and CAED using VVG paradigm showing increased FC network in CAED (a) compared to COAED (b)

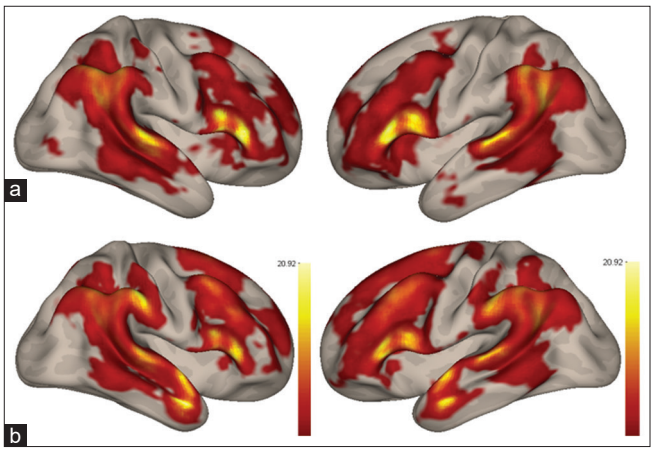

Figure 4: Compared to COAED (a), CAED (b) shows increased functional connectivity for left frontal and temporal areas in Seed-to-voxel FC ($P < 0.001$)

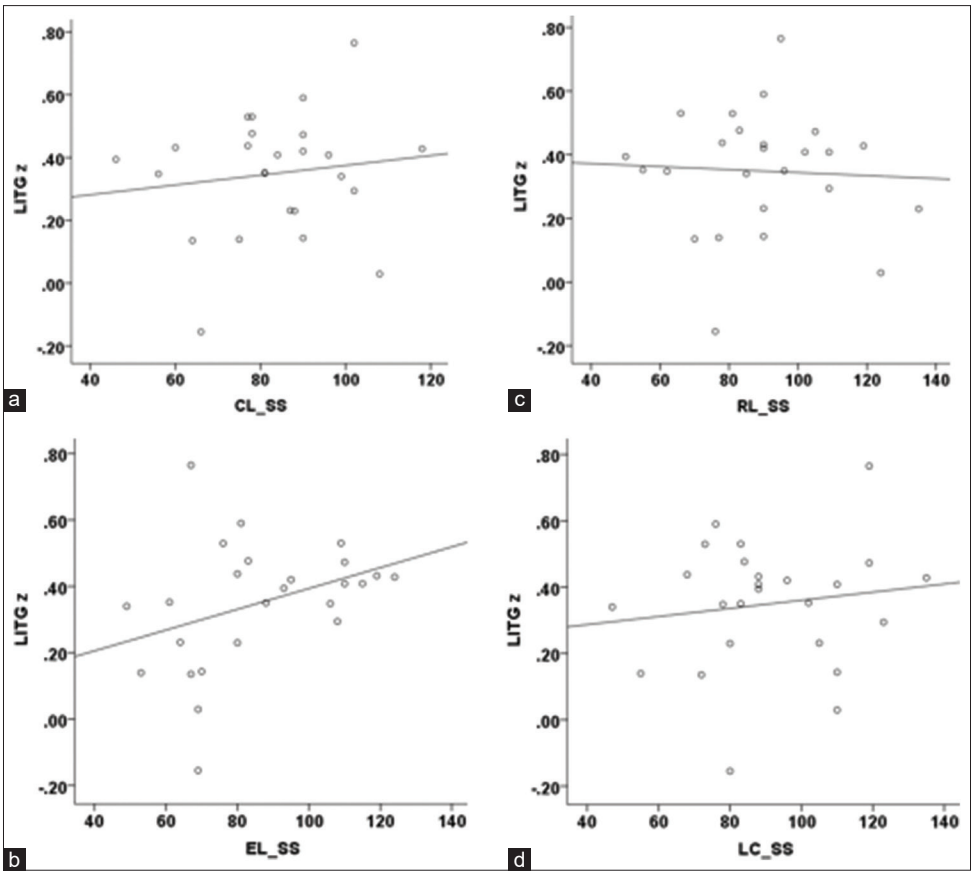

Figure 5: A positive trend was seen between FC z score and language function tests-CL_SS, EL_SS, RL_SS, and LC_SS, though not statistically significant. (CL_SS: Core language standard score; EL_SS: Expressive language standard score; RL_SS: Read language standard score; LC_SS: Language content standard score)

CAED. The details of antenatal AED exposure, maternal epilepsy syndrome, and the neuropsychological and language development assessment data were prospectively collected for all the subjects in the registry. Their malformation outcome, neuropsychological and language function at different ages,[4,5,9] and brain volume changes[6] have been published earlier. In the present study, we had compared the FMRI FC data of CAED and COAED.

Functional network connectivity changes in CAED

FC represents functional interactions between different regions of the brain based on a BOLD reaction in the resting state as well as during task activation. FMRI with FC provides new insight into a noninvasive method for studying brain connection *in-vivo*.[10] The key observations in our study are that children with exposure to AEDs in utero had impaired neuropsychological and language functions and their fMRI showed significantly stronger functional language network connectivity compared to unexposed children—COAED. They demonstrated increased FC between frontal and temporoparietal areas. The COAED group had strong FC between precise nodes on either hemisphere as well as nodes within the same hemisphere. In contrast to that, the CAED showed increased FC between more number of nodes spread over ipsilateral and contralateral hemispheres. The maximum connectivity was seen between frontal language areas in CAED, while in COAED, it was between temporoparietal language networks. This could represent the more involvement of frontal connectivity networks in the exposure group for producing a particular language function.

Recent studies have shown that the ontogeny of FC starts as widespread connectivity in language areas in normal children.[11,12] Similar FC maturation had been described in animals.[13] It appears that the language functional connectivity starts as widespread connectivity that later matures into FC between discrete nodes as the individual's language functions evolve. The FMRI and connectivity differences observed in CAED could be a compensatory mechanism or a biomarker of their language dysfunction. Increased resting network connectivity has been described with many disorders in children and adults like autism,[14-17] dyslexia,[18,19] depression,[20] and attention deficit hyperkinetic disorders (ADHD).[21] The resting network connectivity involving basal ganglia and thalamus[16,17] or caudate nucleus and other regions had been reported to be increased in autism.[22] Abnormally disrupted FC was also described with prenatal exposure to other toxins like alcohol[23,24] and cocaine.[25] The variations in FC observed in prenatal exposure to toxins, neurobehavioral disorders, ADHD, and dyslexia point toward inappropriate and incomplete

pruning of the neural networks specific for language and augmentation of supplementary connectivity through visual or other mechanisms.

The present study has important implications. This is the first documentation of abnormal fMRI and FC in children exposed to AEDs in utero. This study has demonstrated abnormal functional connectivity in CAED that could possibly explain the clinical and phenotypic characteristics. The prenatal exposure to AEDs may interfere with the development of normal network connectivity as demonstrated with antenatal exposure to alcohol or cocaine.[23-25] AEDs are also known to cause disordered cell maturation and apoptosis.[26] It calls for more further longitudinal studies involving a large number of subjects and many AEDs to look into differential effects of different AEDs, their dosage, and timing of exposure.

The strength of the study comes from the reasonably robust methodology used for the FC analysis and the selection of exposure group from a robust pregnancy registry. The main limitation of the study was the small sample size that restricted the scope for analyzing the effects of different AEDs or maternal seizures in the child's language network connectivity. Since there were no left-handed children in this series, the hemispheric lateralization could not be studied. We used the seed-based connectivity analysis involving selected language areas only. There may be network connectivity to other language association areas or other brain regions which were not addressed.

Conclusion

The study has demonstrated abnormal functional connectivity that underlies the clinical and phenotypic characteristics. The AEDs may be interfering with the development of normal network connectivity. This finding is in agreement with the observation with antenatal exposure to substance abuse like alcohol, cocaine, etc. All these are known to interfere with neuronal maturation and organization. AEDs are also known to cause apoptosis. It calls for more further studies to look into the differential effects of different AEDs, their dosage, and timing of exposure.

Our observations in CAED with antenatal AED show that these children utilize more temporoparietal language areas and frontal connectivity network for verbal language function, which might be defective language systems, that is overreacting as a compensatory mechanism.

Our FC analysis provides new insight into the abnormal neuronal integrity in CAED which needs to be supported with further studies with a large sample size and involving multiple AEDs.

Ethical standards

We declare that the present study has been approved by the SCTIMST Ethical Committee (Institutional Ethical Committee Reference Number -IEC/300] and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

We declare that all patients and controls gave informed consent prior to inclusion in this study.

Declaration of patient consent

Informed consent was obtained from all individual participants included in the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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