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Language lateralization in pre-adolescent children: FMRI study using visual verb generation and word pair paradigms

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Abstract

Background: FMRI is a noninvasive tool for mapping language networks, especially in children. We conducted FMRI studies in children in the age group 8- 12 years using 2 different paradigms for assessing language networks and lateralization. **Aim:** To map language networks in pre-adolescent children and to calculate lateralization index using two different visual paradigms. **Methods and Materials:** The study was conducted in normal right handed children in the age group 8-12 years. Sixteen normal subjects underwent FMRI using 2 paradigms- visual verb generation (VVG), word pairs paradigm (WPP) to stimulate language areas. FMRI data analysis was done using SPM8 (statistical parametric Mapping) software. Total activated voxels were calculated for each hemispheres in the pre-defined ROIs for both paradigms. **Results:** FMRI showed left language lateralization in 13 out of 16 children with both VVG and WPP and bilateral language lateralization in two subjects. With VVG there was more significant activation in the left inferior triangular gyrus (ITG) ($P < 0.001$), left inferior opercular gyrus (IOG) ($P < 0.01$), left middle frontal gyrus (MFG) ($P < 0.05$), left and right dorsolateral prefrontal cortex ($P < 0.05$). Left posterior superior temporal gyrus (STG or WA) ($P < 0.001$), Left AG ($P < 0.03$), Left SMG ($P < 0.05$) were significantly activated with WP paradigm. **Conclusion:** Our FMRI studies showed that VGP predominantly activated frontal language areas and WPP predominantly activated temperoparietal language areas. Several other brain regions were also involved in language processing apart from the classical language areas.

Key words: Functional magnetic resonance imaging; language lateralization; pre-adolescent children

Introduction

Functional magnetic resonance imaging (FMRI) is a well-known comprehensive noninvasive tool for mapping blood oxygenation level changes associated with functional neuronal activity.[1] FMRI has been extensively used for both clinical and research purposes. It is used for assessing regional brain activation changes associated with specific language, sensory, motor, and cognitive tasks.[2-4] It is widely used for mapping eloquent regions of brain for presurgical evaluation in patients with brain tumors, epilepsy, cortical dysplasia, and so on.[5]

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Language lateralization in humans is a unique function with most showing left hemispheric lateralization. It has been shown by FMRI that 95% of right-handed and 60–75% of left-handed individuals have left hemispheric lateralization. Few FMRI studies with regard to language have been published in children with high success rates.[6-9] FMRI studies in children provide a platform for understanding a wide array of neuronal pediatric pathologies in children as language is one of the earliest function to develop in children. Literature had shown that FMRI studies in children have high degree of accuracy and success rates comparable to adults.[9-11]

In this study we used FMRI to understand language lateralization in children using two language paradigms – verb generation task and semantic paradigm task. The advantages of FMRI in children are that it is noninvasive, has no radiation exposure, and can be repeated for reproducibility. However, it can prove to be difficult in uncooperative patients.

Both paradigms were simple enough for children but sufficiently comprehensive to stimulate language areas. Our objective was to compare language lateralization in normal children using these two different language paradigms. Verb generation is known to stimulate Broca's area (BA) and word pair task is known to stimulate Wernicke's area (WA) more compared to other language areas.[11] We hypothesized that verb generation task could produce more robust language activation compared to word pair task in children. We also aimed to calculate lateralization index using these two paradigms independently. Only few studies have been conducted on FMRI at this young age in India.

Materials and Methods

Study participants

Study design

The protocol was approved by the institutional Ethical committee, and written informed consent from the parents and assent forms from the children were obtained. All right-handed children were taken for the analysis. Sixteen right-handed children with Malayalam (vernacular language) as mother tongue in the age group 8–12 years were selected. Children with metabolic disorders, psychiatric illness, and history of any acquired neurological insult, head injury, congenital malformations, visual problems, and metallic implants were excluded from the study. Children who were fluent in Malayalam language, had normal vision, hearing, and with normal brain MRI were enrolled for the study purpose.

Magnetic resonance imaging protocol and analysis

The structural whole-brain imaging was done using neurovascular head coil with soft pads placed around the head to immobilize the head after training them to reduce movement artifacts. The MRI was performed using 1.5 Tesla magnetic resonance scanner (AvantoSQ engine, Siemens, Erlangen, Germany). For precise anatomical evaluation, a three-dimensional (3D) Fast Low Angle Shot (FLASH) sequence, which is a high-resolution 3D T1 weighted images of brain, was obtained [repetition time/echo time (TR/TE) 11/4.94 ms, flip angle 15°, field of view (FOV) 256 mm, slice thickness 1 mm, and matrix of 256 × 256]. A 3D Fluid Attenuated Inversion Recovery (FLAIR) sequence (with TR/TE/TI 5,000/405/1,800 ms, FOV 256 mm, slice thickness 1 mm, matrix 256 × 256) was acquired in axial plane to evaluate for 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; number of slices – 36; with slice thickness 3 and 0 mm gap.

Functional magnetic resonance imaging paradigm

Before the start of the procedure, detailed description of the paradigms was presented to the subjects. The protocol of the study was described elsewhere.[11] Visual verb generation (VVG) and word pair paradigms (WP) were presented visually to stimulate language areas. It is a block design paradigm consisting of alternating blocks of five active and five rest conditions, each block consisting of 10 measurements and lasting 30 s. The total acquisition time was 6 minutes. A total of 100 measurements were obtained per session.

VVG: In VVG, a stimulus was presented visually through a small MR compatible screen in front of the participants. This screen was connected to MRI console. The pictures of noun were shown to the child who had to silently generate the corresponding noun shown in the screen. During the rest phase, cross wires were shown [Figure 1A]. Each paradigm lasted for 6 min.

Word pair semantic paradigm (WPP): In this paradigm, related and unrelated words were presented in active phase, through a small screen in front of them. During the

Figure 1 (A and B): Visual Verb Generation Paradigm (A) and Word Pair paradigm (B) presented visually in a screen in front of subjects inside the MRI scanner

rest phase, meaningless patterns were shown [Figure 1B]. The children were instructed to press the right-handed button (if they considered that the words shown were related) or the left-handed button (if they considered that the words were unrelated). This helped to verify that the children were following the paradigms correctly. Both these paradigms were shown using a laptop connected to an MR workstation and synchronized with image acquisition.

Group 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 motion corrected and realigned, then co-registered to high-resolution structural T1-weighted image – T1MPR and normalized to Montreal Neurological Institute template provided in the SPM8 toolbox. After normalization, the images were smoothened with $8 \times 8 \times 8$ mm^3 full-width half-maximum Gaussian filter. These images underwent first-level analysis whereby five active and five rest conditions were incorporated in the design matrix along with other regressors, such as movement, and filtered using a filter cut-off of 128 s. The total acquisition time was 6 min for each paradigm.

Then the images underwent a second-level analysis and one sample *t*-test was performed. For each subject and for each paradigm, the number of activated voxels in both hemispheres were calculated. Images were thresholded at a given value and only voxels at which all images exceeded threshold of 30 were included by subtracting rest condition from active condition with corrected $P < 0.05$. Total number of significantly activated voxels were measured in each hemisphere in the predefined region of interests (ROIs) in frontal, temporal, and temporal lobes corresponding to the anatomically known language areas – inferior frontal gyrus (IFG) of frontal lobe, superior temporal gyrus (STG), supramarginal gyrus (SMG), and angular gyrus (AG) of the parietal lobe were selected. These areas corresponded to motor speech area, sensory speech area and speech association areas.

FMRI laterality index (FMRI-LI): Total activated voxels in the left ROI (LHV) and the right ROI (RHV) were calculated for each individual in both hemispheres and for each paradigm separately by two authors – RMS and JSJ. The mean value of activation from each examiner was taken. The laterality index (LI) was calculated from the formula LI = (LHV − RHV)/(LHV + RHV). LIs with ≥+0.1 value indicate left hemispheric lateralization and ≤ −0.1 indicate rightward asymmetry, and those values between +0.1 and − 0.1 represent bilateral lateralization.[12]

Results

Demographic characteristics

There were 6 males and 10 females in our study group. The mean age was 10.66. All subjects successfully completed FMRI studies.

Functional magnetic resonance imaging

Overall voxel activation

All subjects showed significant bold activation in language areas as well as language association areas [Table 1].

With VVG there was more significant activation in the left inferior triangular gyrus (ITG) ($P < 0.001$), left inferior opercular gyrus (IOG) ($P < 0.01$), left middle frontal gyrus (MFG) ($P < 0.05$), left and right dorsolateral prefrontal cortex ($P < 0.05$) [Figure 2A] compared to right side. Other areas which showed significant activation during VVG were bilateral cuneus ($P < 0.001$), left superior parietal lobule (SPL) ($P < 0.05$), left SMG ($P < 0.04$). In few subjects (2/16), there was activation of anterior cingulum, bilateral lentiform nucleus, and left WA (4/16).

WPP: Left posterior STG (STG or WA) ($P < 0.001$), left AG ($P < 0.03$), and left SMG ($P < 0.05$) were significantly activated in WPP. There was also activation of bilateral cuneus and lingual gyri ($P < 0.001$), left SPL ($P < 0.04$). In few subjects (5/16) along with WA activation, BOLD signals were also demonstrated in BA and left MFG. Bilateral activation in WA is seen in 2/16 subjects [Figure 2B].

Hemodynamic response function curve

The hemodynamic response function (HRF) response patterns fitted well with experimental blocked design model for VGP and WPP [Figure 3A and B].

Hemispheric lateralization

VVG: FMRI showed left hemispheric lateralization in 13 children. Rest (n = 2) showed bilateral hemispheric

Table 1: FMRI activation areas during VVG and WPP

Paradigm	Areas of activation	MNI co-ordinates	Cluster size (mm^3)	Z size	P
VGP	L-IOG	44.48 16.23 14.00	898	6.98	0.001
	L-ITG	-44.6 30.44 0.55	652	5.86	0.001
	L-MFG	-46.34 26.75 25.04	322	3.87	0.023
	L-PMA	-40.72 36.82 18.64	314	3.33	0.032
	R-INSULA	44.6 16.2 0.55	157	3.25	0.043
	R-ITG	46.73 30.44 0.55	148	3.12	0.044
WPP	L-SMG	-56.25-40.21 35.87	888	7.32	0.001
	L-AG	-52.8-58.09 33.16	563	7.36	0.001
	L-MFG	-42.22 22.83 20.63	453	5.23	0.002
	L-I TG	-45.83 35.39 20.38	398	4.23	0.012
	L-PMA	-40.23 30.28 20.12	231	3.33	0.011
	L-PHG	-26 0.2-36-10.4	239	3.12	0.042

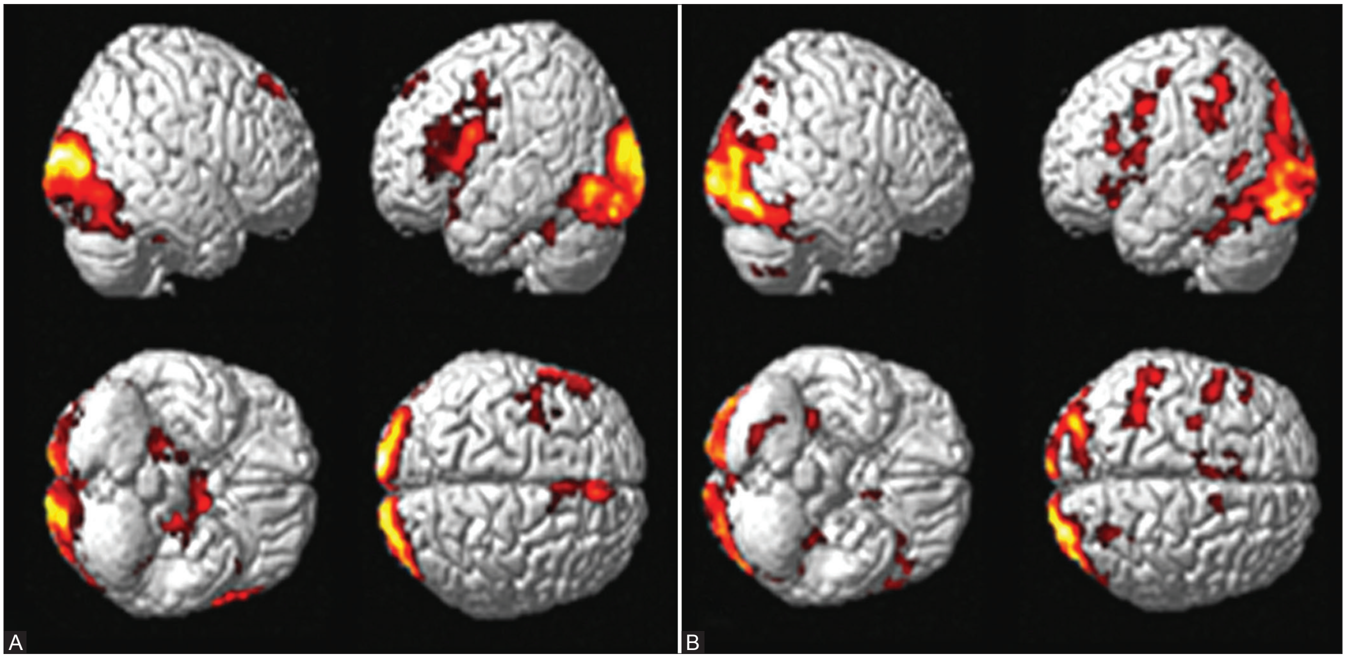

Figure 2 (A and B): Glass view brain showing group analysis of activated voxels of 16 subjects for fMRI during (A) VVG in the inferior frontal gyrus corresponding to Broca's area, (B) WPP in superior and middle temporal gyrus corresponding to Wernicke's area with some acyivation in Inferior frontal gyrus, Middle frontal gyrus, dorsolateral prefrontal cortex and few activation in ventral occipito temporal areas

lateralization and right hemispheric lateralization in 1 subject. Total number of activated voxels in left hemisphere were 1439.84 ± 1543 and right hemisphere were 914.375 ± 962. There were increased activation in IFG (BA), MFG, premotor area posterior STG (WA), SMG, and AG. VVG produced more activation in IFG than STG. In few subjects (3/30), there was activation in the SPL bilaterally.

WPP: In 10 subjects, WPP produced more significant activated voxels in WA (PSTG) than BA (IFG). Few significantly activated voxels were seen in SMG, AG, and MTG. In 6 subjects there were more activation of BA compared to WA. The mean total activated voxels on left side were 1508 ± 1384 and on right side were 998 ± 1074.

LI: In VVG the LI of the subjects varied between −0.18 and 0.63 with a mean of 0.25 ± 0.19. One subject had shown right hemispheric lateralization of −0.18 and 2 subjects had bilateral lateralization with LI of 0.09. With WPP for 16 subjects, the mean LI was 0.26 ± 0.27 in the range of −0.08 (right lateralization) to 1 (strong left lateralization). There was no significant change in the LI calculated using VGP and WPP ($P = 0.0892$) [Table 2].

Table 2: FMRI findings in visual verb generation paradigm (VGP) and word pair paradigm (WPP) with total number of activated voxels in the ROI (extended threshold>30 and t>3) and Laterality Index using VGP (LI-VGP) and WPP (LI-WPP)

Subjects	No of activated voxels using VGP		No of activated voxels using WPP		LI-VGP	LI-WPP
	L	R	L	R		
1	160	230	392	320	-0.18	0.1
2	347	289	716	629	0.09	0.06
3	245	129	798	287	0.31	0.47
4	2000	1276	2789	2291	0.22	0.1
5	3050	2120	2819	817	0.18	0.55
6	280	210	782	563	0.14	0.16
7	5248	2918	1627	1928	0.29	-0.08
8	3281	2109	2781	1532	0.22	0.29
9	2133	1207	1829	928	0.28	0.33
10	165	89	209	0	0.3	1.0
11	213	105	291	221	0.34	0.14
12	198	45	1392	420	0.63	0.54
13	2689	1763	5426	4210	0.21	0.13
14	325	182	726	526	0.28	0.16
15	529	129	256	182	0.61	0.17
16	2176	1829	1298	1129	0.09	0.07

Discussion

Language is a function unique to human beings. Precise localization of language areas is essential to prevent or reduce damage to these eloquent areas during respective surgical procedures for epilepsy and several other conditions. Although several methods such as intracarotid amytal test, intraoperative cortical electrical stimulation, and magnetoencephalography are widely used for mapping language areas, FMRI is best suited for the noninvasive imaging of language areas with good reproducibility.[13-16]

The present FMRI study aimed to identify language processing areas in the brain in pre-adolescent children during VGP paradigm and WPP. We utilized FMRI to map cortical language areas in normal right-handed individuals. Both the paradigms produced strong activation in the motor and sensory language areas. There was no significant correlation between age and activated voxels of left (P = 0.148, R^2 = 0.144) or right language areas (P = 0.130, R^2 = 0.13) though there was a positive trend with both. With VGP there was more activation in the bilateral ITG and IOG, and dorsolateral prefrontal cortex and MGF with more significant voxels on the left side. Few significant activated voxels were also seen in left STG and SMG. During VVG the child was asked to think about the verb when the noun was projected visually in the screen. This involved both word production as well as comprehension. Hence in all subjects it produced activation of classical BA (left ITG, IOG) with some activation of the WA as well as speech association areas. Studies have also shown the importance of VVG to evoke language areas in the brain. It is one of the widely accepted paradigms used for underpinning language areas in the brain.[9,12]

In WPP, related and unrelated noun pairs were represented visually through the screen and a response button given to child. It resulted in classical pattern of activation in left posterior STG. The activation was also seen extending to involve posterior MTG, bilateral hippocampus, planum temporale with activation of ventral temporo-occipital cortex. There were increased activation voxels in the ITG, IOG, with spreading to involve MTG and STG. In 63% of the subjects with WPP, more activation were seen in the posterior temporal STG, MTG, SMG, and AG, with more significant voxels on the left side. While in 37%, more activation were seen in left IFG and MFG with some activation in the temporoparietal language areas. Hence with WPP, there were more diffuse activation of language and language association areas compared to VVG, where it produced more localized and robust activation in frontal region.

As expected, there was strong left hemispheric lateralization with both paradigms in 13 out of 16 subjects and involved areas in the frontal, temporal, and parietal lobes. This is in concordance with other language FMRI studies in children and adults.[17-19] Positron emission tomography (PET) studies have also confirmed the extensive temporoparietal, orbitofrontal areas involved in language processing.[20,21] Less expected areas include SPL, inferior parietal lobule, MTG, fusiform gyrus, and cerebellum. In frontal lobe, few clusters were seen in motor area, premotor areas. Though the precise role of cerebellum in language comprehension is not well established, both FMRI and PET studies have pointed that the cerebellum plays a key role in language computation and processing, especially the right cerebellar hemisphere.[22,23]

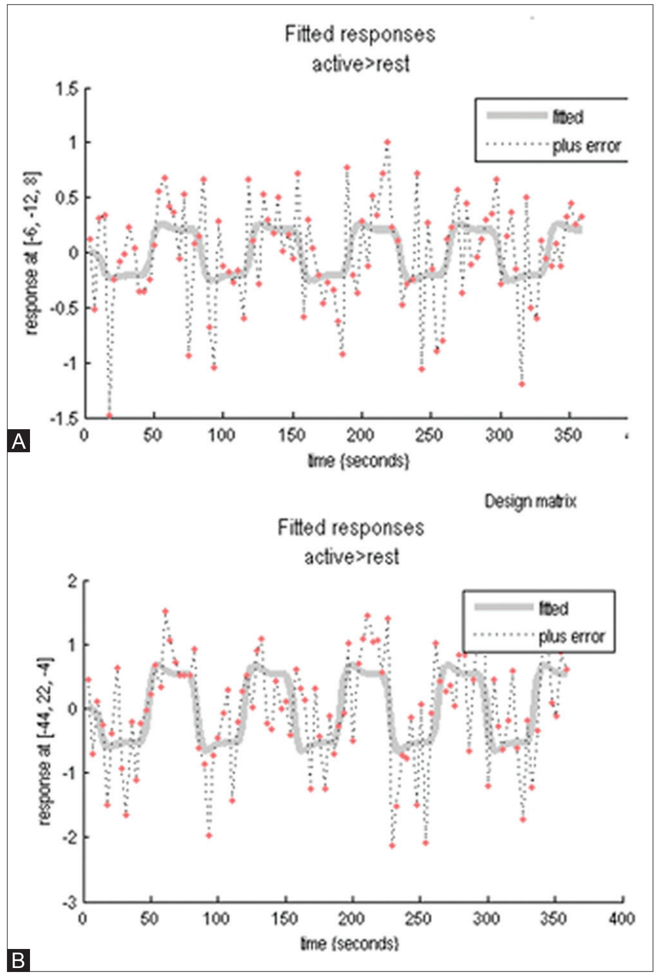

Figure 3 (A and B): HRF curve (Hemodynamic Response Function) with (A) Visual Verb Generation Paradigm and (B) Word Pair paradigm

For calculating LI, we used predefined ROI involving accepted language areas – IFG, STG, MTG, AG, and SMG. This included primary language and language association areas and hence, voxels activated in these regions were calculated for the LI. This methodology is known to stimulate language areas.[15,16] We got significant positive correlation with WPP-LI and age (P < 0.02), though with VGP-LI there was a positive trend with age that was not statistically significant (P = 0.089). Numbers of activated voxels above a statistical threshold were selected for LI (with z-scores >3). Studies have shown that threshold-dependent activation calculation was more specific.[24,25] Mean total activated voxels were more with WPP than VGP.

The study had several limitations of which most significant was the small sample size. Moreover, we selected all right-handed individuals for language processing. Hence we were not able to compare the language activation patterns between left-handed and right-handed individuals or bring out the varied activation patterns in left-handed individuals. We also did not study the pattern associated with auditory language paradigms.

Conclusion

FMRI studies using two visual language paradigms have yielded language lateralization that is comparable with other PET and FMRI studies. Both paradigms were good and robust in stimulating language areas with no significant differences between them. VGP predominantly activated frontal language areas and WPP predominantly activated temporoparietal language areas.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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