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Functional Imaging of Broca's Area in Native Persian Speakers: An fMRI Study

Background/Objective: The problem of localization of speech associated cortices using non-invasive methods has been of utmost importance in many neuroimaging studies, but the results are difficult to resolve for specific neurosurgical applications. In this study, we used fMRI to delineate language-related brain activation patterns with emphasis on the Broca's area during the execution of two Persian language tasks.

Patients and Methods: The subjects comprised of nine healthy right-handed men who participated voluntarily in this study. They performed two consequent fMRI paradigms namely; "Word Production" and "Reverse Word Reading". The fMRI data were collected and analyzed. Then, functional images were registered to anatomical images using FSL software. The laterality indices were also calculated in regions of interest with different threshold levels.

Results: The results indicate that Broca's area, as the classical language-production center, was robustly activated while performing these two tasks. In eight out of nine subjects, the left hemisphere dominancy and Broca's area activation were observed and in one case activation was prominent in the homologous area in the right hemisphere.

Conclusion: Similar pattern of cortical activation during Persian word production and Anglophone languages such as English was revealed. fMRI is a valuable means for brain mapping in language studies.

Keywords: Broca's Epicenter, Word Production, Reverse Word Reading, fMRI, Laterality Index

Introduction

Functional Magnetic Resonance Imaging (fMRI) using the blood oxygen level dependent (BOLD) technique employs intrinsic signal changes accompanying sensory and motor stimulation to map brain functions.[1] Consequently, in many recent studies, fMRI has been used to delineate primitive and/or higher cortical functions such as language processing in healthy subjects as well as patients with neurological problems.[2]

On the other hand, clinically, it is crucial to determine the dominant hemisphere for language and brain regions involved in language-associated functions. It is also of great importance to preserve the language-related centers in Brodman's areas of 44 and 45 (classical Broca's area) in patients with frontal lobe tumor or in candidates for drug-resistant epilepsy surgeries. Therefore, a sophisticated preoperative investigation is needed to unravel this critical area.[3] Various approaches such as direct cortical stimulation with intra-operative recording,[4] Wada procedure,[5] and positron emission tomography (PET),[6] have been used to meet this goal. However, non-invasive methods like fMRI are being examined to serve the purpose. Previous studies have employed fMRI to determine language dominancy[7] and also critical language areas like Broca's area,[8] not only in healthy subjects, but also to identify language cortices in neurosurgical patients with vascular malformations,[9] intractable epilepsy,[7,10] and cortical brain tumors.[11,12] Several reports have implemented different statistical methods and different paradigms, such as picture-naming, simple word reading, word generation, verbal fluency, sentence generation, auditory responsive naming, sentence comprehension, sentence repetition, lexical decision, rhyme detection and/or semantic categorization, alone or in combination.[7-21] The reported results on fMRI studies performed on patients and/or healthy subjects are controversial and the possible contribution of the data for surgical applications has to be verified.

One important milestone to achieve optimal contrast in functional images is appropriate task selection.[22] In addition, variation in the subject's language could possibly alter the functional activation patterns.[3,13] As far as we know, no documented fMRI study is available on subjects whose native language is Persian.

The major objective of this study was to implement two newly developed lexico-semantic tasks namely "Word-Production" (WP) and "Reverse Word Reading" (RWR) in native Persian speakers to reveal the epicenter of Broca's area. The data set analysis was performed using FSL software with different threshold levels.

Patients and Methods

Nine healthy right-handed male university students with a mean age of 23 (range: 20–28) years participated in this experiment. The subjects were native Persian speakers with normal vision and their handedness was determined based on Edinburgh Handedness Inventory (mean laterality quotient was +73.3 [range: +45 to +90]).[23]

The stimuli were projected from the other side of the curtain by a video projector employing Presentation™ software (ver 0.6). The procedure of 30-min presentation of the stimuli was kept the same for all subjects. All patients were provided with detailed information about safety of fMRI.

Two Persian lexico-semantic tasks were implemented as fMRI paradigms, namely WP and RWR. The two simple subtraction block-design tasks consisted of six blocks of three rests and three activations with the duration of 30 sec for each block (each task was presented in three min). The stimuli were presented randomly in each case.

The stimuli in each activation block of the WP task consisted of six-word trials. In each "5-sec trial," the subject was exposed with a 4-letter Persian word, letter by letter from right to left (in the right order). Each letter replaced the previous one with an interstimulus interval of one sec. Then, the subject had to read the 4-letter word silently during a five sec interval in each trial. Throughout the rest block, a neutral symbol such as an asterisk or slash was presented to the subject randomly to subtract visual activation.

The stimuli of RWR task in each activation block consisted of 12-word trials. In each "2.5-sec trial," the subject was exposed with a 5-letter Persian word, while letters were presented in the reverse order. They were asked to read each word silently. The rest blocks were similar to the previous task (WP).

MRI apparatus was a 1.5-Tesla GE® Sigma model scanner. A T1W spin-echo sequence was used to generate high-resolution structural maps of the subject's brain with the same dimension and orientation of the functional images. The fMRI data were obtained employing a gradient echo/echo planar imaging (EPI) protocol (TE=60 ms, TR=3000 ms, flip angle=90°, field of view=25 cm^2, number of slices=8, slice thickness=8mm). Image acquisition included eight contiguous axial slices, relatively parallel to the "anterior commissure-posterior commissure" line according to Talairach atlas,[24] beginning from the base of the brain. During each 30 sec of rest or activation, 10 images were acquired every three sec for eight different slices.

Data analyses were carried out using FEAT program (fMRI Expert Analysis Tool, ver 5.1) as part of FSL (FMRIB Software Library) software release 3.2 β.[25-27] Statistical preprocessing procedures were applied to remove motion artifacts, improve signal to noise ratio (SNR), and remove drifts from the raw data.[26-27]

Statistical analysis: Time-series statistical analysis was also carried out using FILM Prewhitening (FMRIB Improved Linear Model) to make the statistics valid and maximally efficient. The corresponding BOLD-signal was characterized by "Z-stat," being a transformation of t statistics, i.e., dividing the parameter estimate by its standard error.[28] Finally, cluster-thresholding was carried out to reveal clusters that were activated significantly. Only clusters with Z-stat > 1 and cluster p threshold less than 0.05 were assumed to be significant. Each cluster was assigned with a particular color in an ascending order and the resultant color voxels were gathered in the so-called functional maps.

Image registration: Z statistic maps (functional maps) were normalized and registered to the standard space as well as anatomical MR images to show major activation foci and to determine their exact sites.[29] This automated intensity-based image registration was carried out by FLIRT program.[28]

Region of interest and post-statistical analysis: Regions of interest (ROIs) were defined for each subject/task separately using BrainMap™ databases established by probability density estimates of functional cerebral loci.[30,31] ROIs were the major cerebral areas known for language processing including: 1- Broca's area and its homologous in the right inferior frontal gyrus. 2- Primary motor cortex (PMC), 3- Supplementary motor area (SMA), 4- Temporal cortex including Wernicke area.

Accordingly, in our analysis, for each ROI, clusters with a Z-stat more than 1 were selected. In each cluster, voxel density of regions with various activation thresholds as well as their mean activation level were calculated.

Indices and other statistical analysis: Lateralization index (LImag) was calculated by density of significantly activated voxels and mean of activated voxels in ROIs instead of the whole hemisphere.[32]

This equation yields LIs values between +100 (strong left hemisphere dominance) and -100 (strong right hemisphere dominance). LIs were subsequently ranked as left hemisphere language dominant (defined as LI>20), co-dominant ($-20 \le LI \le +20$) or right hemisphere dominant (LI<-20).[33]

Assuming Broca's area as the main ROI, the Cartesian coordinates of the center of gravity of the activation volume was calculated and nominated as the epicenter of Broca's area. Mean Z-stats were calculated for each task separately and then compared. The mean of X, Y and Z values for three Cartesian coordinates of the epicenters were compared using Student's t test as well as the corresponding Z-stat. A P value less than 0.05 was considered statistically significant.

Results

Task performance and activation curve

All subjects who participated in the pre-trial phase were able to perform the task properly. They all accomplished the required tasks successfully and the data were obtained and analyzed with FSL software.

For each subject the LImag was calculated according to Matthews et al. formula.[32] The LIs for Z-stat>1 and Z-stat>2.2 were calculated separately. The mean LI for WP with Z-stat>1.0 was 37 and with Z-stat>2.2 was 39.7. The mean LI for RWR with Z-stat>1.0 was 31.9 and with Z-stat>2.2 was 44.7. Employing two different threshold levels yielded a higher laterality index with Z-stat>2.2.

The preprocessing of the data file with FSL yielded a related curve for each activated voxel over the corresponding paradigm consisting of activation and rest blocks.

Patterns of cortical activation

Eight out of nine subjects who participated in the experiment had LI>+20 (left hemispheric activation), while one (subject 4) had LI<-20 (right hemispheric activation). A robust cortical activation of the classic language regions of Broca's area in the left inferior frontal gyrus was obtained in eight subjects in both tasks. In one subject the activation for WP task was bilateral with much higher intensity in the right hemisphere, but for RWR task, Broca's homologous area in the right hemisphere was activated. The obtained functional images of subject 8 for WP and RWR tasks are illustrated in Figures 1 and 2.

Other major activated areas with Z-stat >1 include temporal gyrus in 11 subject/tasks, occipital lobe in seven, right inferior frontal gyrus in six, PMC in four, prefrontal area in four and SMA in three subject/tasks in addition to Broca's area.

Epicenter of Broca's Area:

The epicenter of Broca's area was calculated for each subject/task and mapped on a two-dimensional Talairach grid. The results indicated an inter-subject variation for the epicenter of Broca's area. The epicenters of activated Broca's area in eight subjects are shown in a scattered diagram over the Talairach grid. A comparison of the activation patterns with respect

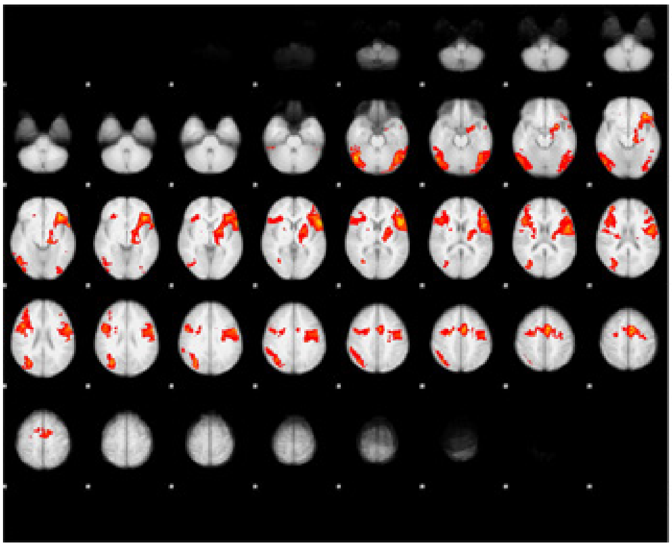

Fig. 1. Typical activations during Word Production task: Axial sections of functional MR Images from subject 8 (26-year-old right-handed man) registered to standard space with FSL software. Word Production were analyzed with Z-stat >2.2. Results show prominent activation of Broca's area in left inferior frontal gyrus.

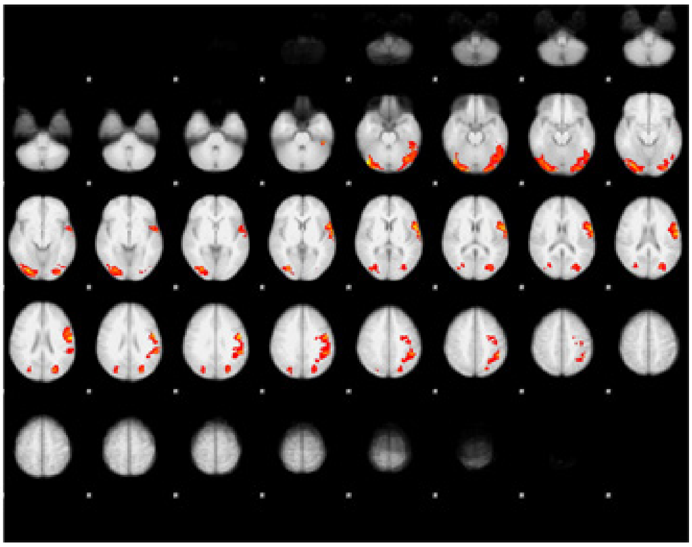

Fig. 2. Typical activations during Reverse Word Reading task: Axial sections of functional MR Images from subject 8 registered to standard space with FSL software. This task also analyzed with threshold, Z-stat >2.2.

to the epicenters of Broca's area indicated that both tasks activated the same topographic areas with approximately the same mean Z-stat ($p<0.05$).

Discussion

A number of advantages and limitations have been suggested for language fMRI over other functional imaging methods. One advantage is that fMRI is a non-invasive technique and allows serial application on a single individual with high spatial resolution.[3] One major problem with language fMRI is "multiple simultaneous activations" which makes it extremely difficult to extract areas that are truly related to the function. Another major problem is spatial "inter-individual variability" with similar paradigms addressed in previous studies.[12,13,18,34,35]

The selection of improper tasks may affect the obtained functional images by inducing "multiple simultaneous activations".[34] This may cause ambiguity and uncertainty in differentiating "eloquent" and "silent" brain regions.[35-37] Therefore specific tasks such as WP and RWR may specifically activate Broca's area. In addition, since classical Broca's area is considered a relatively large part of the cerebral cortex containing both Brodman's areas 44 and 45, it is of great importance for us to mark out its epicenter.

Our results establish that WP and RWR tasks successfully activated lexical language areas especially in the Broca's area (Z-stat>2.2), with acceptable inter-individual variability. Although the tasks were carried out for native Persian speakers, the pattern of activation in other languages may be the same.

Both of the tasks employed in this study (WP and RWR) activated the same area in the main ROI (Broca's area) with epicenters, slightly apart. The foci of activation level of the employed tasks in the study are suggesting the sufficiency of obtaining optimal images if they are considered as a panel. The obtained functional images in our study were superior to those retrieved in studies using object naming, word reading and word generation with multiple linguistic components. This may reflect a more lexico-semantic specificity of WP and RWR tasks.

Another major problem regarding fMRI language analysis is the selection of appropriate threshold for data analysis.[22,38] Selection of a sub-optimal threshold level can cause unacceptable spatial variability in activated brain regions as well as LIs. By increasing the threshold level, eloquent brain areas can be differentiated from silent regions. On the other hand, increasing the threshold level may reduce the sensitivity.[18] Therefore, it is of great importance to develop a method for optimal threshold selection. In fact, we propose that LI changes as a function of the threshold level, and will achieve its most reliable value at the optimal threshold level. At this optimal level, the first derivative of LI function approaches zero and the obtained images would be more valid. However, more cases are required to verify practical application of the suggested "optimal threshold selecting approach."

Finally, the application of the masking technique made it possible to limit the LI calculation in the masked ROI to achieve a more accurate value for LI. In our study we employed "LImag" in the regions of interest to give weight to each voxel according to LI equation.[28,32] We suggest that this index is much more accurate than LI because LImag is a function of both activated voxel density and the corresponding mean Z-stat yielding higher validity for expression of hemispheric dominancy in the ROIs.

In conclusion, it sounds clear that acquisition of more sensitive and specific functional images requires more sophisticated tasks and proper threshold selections. Further research may reveal fine details in Persian processing and better comparison with other languages.

We declare that we have no conflict of interests.

References

1. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H et al. Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci 1992;89:5951-5.
2. Small SL, Burton MW. Functional magnetic resonance imaging studies of language. Curr Neurol Neurosci Rep 2002;2:505-10.
3. Binder JR. Functional MRI of the language system. In: Moonen RCW, Bandettini PA editors. Functional MRI. Berlin: Springer; 2000. p. 406-19.
4. Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 1989;71:316-26.
5. Wada J, Rasmussen T. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance: experimental and clinical observations. J Neurosurg 1960;17:226-82.
6. Thiel A, Herholz K, von Stockhausen HM, van Leyen-Pilgram K, Pietrzyk U, Kessler J et al. Localization of language-related cortex with 150-labeled water PET in patients with gliomas. Neuroimage 1998;7:284-95.
7. Springer JA, Binder JR, Hammeke TA, Swanson SJ, Frost JA, Bellgowan PSF et al. Language dominance in neurologically normal and epilepsy subjects. Brain 1999;122:2033-45.
8. Brannen JH, Badie B, Mortiz CH, Quigley M, Meyerand ME, Haughton VM. Reliability of functional MR imaging with word-generation tasks for mapping Broca's area. AJNR Am J Neuroradiol 2001;22:1711-8.
9. Pouratian N, Bookheimer SY, Rex DA, Martin NA, Toga AW. Utility of preoperative functional magnetic resonance imaging for identifying language cortices in patients with vascular malformations. Neurosurg Focus 2002;13:21-32.
10. Sabbah P, Chassoux F, Leveque C, Landre E, Baudoin-Chial S, Devaux B et al. Functional MR imaging in assessment of language dominance in epileptic patients. Neuroimage 2003;18:460-7.
11. Ashtari M, Perrine K, Elbaz R, Syed U, Thaden E, McIlree C et al. Mapping of functional anatomy of sentence comperhension and application to presurgical evaluation of patients with brain tumor. AJNR Am J Neuroradiol 2005;26:1461-8.
12. Heberg A, Kvistad KA, Unsgard G, Haraldseth O. Preoperative blood oxygen level-dependent functional magnetic resonance imaging in patients with primary brain tumors: clinical application and outcome. Neurosurgery 2004;54:902-15.
13. Baciu M, Juphard A, Cousin E, Le Bas JF. Evaluating fMRI methods for assessing hemispheric language dominance in healthy subjects. Eur J Radiol 2005;55:209-18.
14. Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Frischer M et al. Determination of language dominance using functional MRI: a comparison with the Wada test. Neurology 1996;46:978-84.
15. Fitzgerald DB, Cosgrove GR, Ronner S, Jiang H, Buchbinder BR, Belliveau JW et al. Location of language in cortex: a comparison between functional MR imaging and electrocortical stimulation. AJNR Am J Neuroradiol 1997;8:1529-39.
16. Gillard WD, Balsamo L, Xu B, McKinney C, Papero PH, Weinstein S et al. fMRI language task panel improves determination of language dominance. Neurology 2004;63:1403-8.
17. Ramsey NF, Sommer IEC, Rutten GJ, Kahn RS. Combined analysis of language tasks in fMRI improves assessment of hemispheric dominance for language functions in individual subjects. Neuroimage 2000;13:719-33.
18. Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I. Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. Neurosurgery 2003;52:1335-47.
19. Rutten GJM, Ramsey NF, Van Rijen PC, Alpherts WC, Van Veelen CWM. FMRI-determined language lateralization in patients with unilateral or mixed language dominance according to the Wada test. Neuroimage 2002;17:447-60.
20. Rutten GJM, Ramsey NF, Van Rijen PC, Noordmans HJ, Van Veelen CWM. Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. Ann Neurol 2002;51:350-60.
21. Stippich C, Mohammed J, Kress B, Hahnel S, Gunther J, Konrad F et al. Robust localization and lateralization of human language function: an optimized clinical functional magnetic resonance imaging protocol. Neurosci Lett 2003;346:109-13.
22. Baciu MV, Watson JM, Maccotta L, McDermott KB, Buckner RL, Gilliam FG et al. Evaluating functional MRI procedures for assessing hemispheric language dominance in neurosurgical patients. Neuroradiology 2005;47:835-44.
23. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97-113.
24. Talairach J, Touroux P. Co-planar streotaxic atlas of the human brain. In: 3-Dimensional proportional system: an approach to cerebral imaging. New York(NY): Thieme Medical Publishers; 1988.
25. Smith SM, Jenkinson M, Woolrich MW, Beckman CF, Behrens TEJ, Johansen-Berg H et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23 Suppl 1:208-19.
26. Jenkinson M, Bannister PR, Brady JM, Smith SM. Improved optimisation for the robust and accurate linear registration and motion correction of brain images. NeuroImage 2002;17:825-41.
27. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17:143-55.
28. Adcock JE, Wise RG, Oxbury JM, Oxbury SM, Matthews PM. Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. Neuroimage 2003;18:423-38.

29. Jenkinson M, Smith SM. A global optimisation method for robust affine registration of brain images. Medical Image Analysis 2001;5:143-56.
30. Fox PT, Lanchester JL. Neuroscience on the Net. Science 1994;266:994-6.
31. Nielsen FA, Hansen LK. Modeling of activation data in brain map™: detection of outliers. Hum Brain Mapp 2002;15:146-56.
32. Matthews PM, Adcock J, Chen Y, Fu S, Devlin JT, Rushworth MF et al. Towards understanding language organisation in the brain using fMRI. Hum Brain Mapp 2003;18:239-47.
33. Binder JR, Rao SM, Hammeke TA, Frost JA, Bandettini PA, Jesmanowiscz A et al. Lateralized human brain language systems demonstrated by task subtraction functional magnetic resonance imaging. Arch Neurol 1995;52:593-601.
34. Seghier ML, Lazeyras F, Pegna AJ, Annoni JM, Zimine I, Mayer E et al. Variability of fMRI activation during a phonological and semantic language task in healthy subjects. Hum Brain Mapp 2004; 23:140-55.
35. Yoo SS, Talos IF, Golby IG, Black PM, Panych LP. Evaluating requirements for spatial resolution of FMRI for neurosurgical planning. Hum Brain Mapp 2004;21:34-43.
36. Gitelman DR, Nobre AC, Sonty S, Parrish TB, Mesulam MM. Language network specializations: an analysis with parallel task designs and functional magnetic resonance imaging. Neuroimage 2005; 26:975-85.
37. Price CJ, Mummery CJ, Moore CJ, Frakowiak RS, Friston KJ. Delineating necessary and sufficient neural systems with functional imaging studies of neuropsychological patients. J Cogn Neurosci 1999;11:371-82.
38. Worsely KJ, Liao CH, Aston J, Petre V, Duncan GH, Morales F et al. A general statistical analysis for fMRI data. Neuroimage 2002;15:1-15.