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Toward fMRI Group Identification Based on Brain Lateralization

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Abstract— This research presents a novel application of Lateralization Index (LI) in support of a decision making process for the classification of subjects based on their brain activation patterns using Functional Magnetic Resonance Imaging (fMRI) datasets. The decision process considers the subject grouping based on additional spatial information provided by the LI behavior for each individual when calculated for specific Broca's and Wernicke's language areas. The presented results were obtained applying the LI concept to assess the activation pattern on both control and Localization-related epilepsy (LRE) subjects obtained during the execution of the language network oriented paradigm referred to as the "auditory description decision task" (ADDT). Upon assessing 114 datasets, activation was observed on 103 (90%) of them, while 11 (10%) showed no activation. Among these 103 datasets, 64 (62%) datasets were presumed as control data and 39 (38%) were presumed as LRE data. The data was obtained from 5 different hospitals using the online web-based repository site (mri-cate.fiu.edu). Masks were used for temporal and lateral brain areas for the normal brain, and individual masks were used for 48 Brodmann areas (BA). A t-test yielded a P-value of 0.0151, which indicates a statistically significant difference in the mean of both groups. The LI was also calculated using both native and normal spaces for each subject, and in this case, no statistically significant difference between the two spaces was found. It is observed that the average brain activation intensity on the LRE subjects was higher than the one observed on the control population. On contrasting the LI percentages between control and LRE data (c%, e%), the following groups were identified: a) strong right lateralization: (0%, 18%), b) right lateralization: (2%, 10%), c) bilateral: (20%, 15%), d) left lateralization: (42%, 26%), e) strong left lateralization: (36%, 31%).

Keywords; Activation Pattern; ADDT; Brodmann area, Epilepsy; fMRI; FSL; LI; Medical images; Online multi-site repository;

I. INTRODUCTION

According to the latest report of the Centers for Disease Control and Prevention [1], which involved a multi-state study, it has been found "that about one out of 100 adults have active epilepsy, and more than one-third are not getting sufficient treatment". Since its last complete report in 1995, the Epilepsy Foundation of America has estimated at that time that nearly 2.3 million people suffered from seizure disorders in the United States [2], which has now unfortunately increased to 3 million. This statistic provides insight on the impact of epilepsy in our society today.

Epilepsy is predominantly a childhood disorder, since the mean age of epilepsy onset among epilepsy surgery series is between 8 and 10 years. Approximately 25-30% of chronic epilepsy patients have altered location and lateralization of language processing networks. Clinical experience has demonstrated that the actual location of language functions is difficult to predict, so in order to minimize the risk for post operative language deficits on surgery patients, language networks must be identified for planning epilepsy and tumor surgery [3-7].

Through functional magnetic resonance imaging (fMRI), it has become possible to achieve a better understanding of brain functions through substantially improved spatial and temporal resolutions. Moreover, it becomes also possible to observe visually the spatio-temporal behavior of the brain activation during a normal routine based on the Blood-oxygen-level dependent principle (BOLD) [8-10]. One of the fundamental elements in the functional neuroimaging research is to track and study the spatio-temporal behavior of the activation pattern during the performance of a controlled task.

In our study, the subjects were asked to perform an auditory description decision task (ADDT), where subjects hear a description of an object and decide if that description is correct or not, for instance: "The moon is round". It has been found that this task is a good probe for dominant superior temporal sulcus, but also activates some of the temporal area of the brain [11-13].

There are, however, technical barriers that are yet to be resolved in the application of fMRI. For instance, the concordance with typical language lateralization is high, but the statistical validation with atypical language representation has not been firmly established [4, 14]. A 10% partial discordance between the Intra-carotid Amobarbital Test (IAT) and fMRI has been reported [15].

The lateralization index (LI) is a coefficient used as an asymmetry indicator of activation patterns on the brain, after a subject has performed a specific task. LI provides a metric to compute the brain hemispheric specialization. However, the actual value of the LI is dependant on many factors including but not limited to threshold issues, regional localization of activations, activation voxel intensity, noise, and statistical outliers [16, 17].

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Florida International University (FIU) in collaboration with 16 health care institutions has established a multisite repository for pediatric epilepsy data (mri-cate.fiu.edu) [18-20]. The specific aims that were pursued in this study are:

1. Evaluating the impact of activation *intensity* and *activation extend* in the LI calculations.
2. Assessing the benefit of using two LI values, corresponding to Broca's and Wernicke's regions to classify brain activation results after performing Language Network related tasks.
3. Identifying clusters of activation patterns using the LI values computed for the individual BAs.

Commonly, LI has been implemented using voxel counting or voxel intensity summation; however, there is a debate in the fact that simple voxel counting is prone to ignore important aspects related to the intensity of the activation [16, 17]. Additionally, voxel summation shows the drawback of being very easily influenced by the presence of statistical outliers. In this study, since both concepts have the benefit of complementation, a new approach is thus designed to overcome this problem. Moreover, a new attempt is made at circumventing the problem associated to the lack of spatial information on LI results by analyzing two LI coefficients, which we claim adds spatial information to the final classification results. Besides, in previous studies synthetic and/or limited actual subject datasets were used as opposed to relatively large actual subject datasets used in this study.

II. METHODS

A. Data Collection

A total of 114 fMRI datasets and their correspondent anatomical T_1 MRIs were taken from the data repository mri-cate.fiu.edu. Table I summarizes source institution and the scanner characteristics for the subjects.

TABLE I. SOURCE INSTITUTIONS AND SCANNER CHARACTERISTICS FOR SUBJECTS USED ON THE STUDY.

Institution	Scanner	Subjects	
		LRE[1]	*HC*[2]
HSC Hospital of Sick Children Toronto, CA	GE 1.5T	6	0
MCH Miami Children Hospital Miami, FL	Phillips Intera 1.5 T	6	0
CNMC Children's National Medical Center Washington, DC	Siemens Trio 3T	15	64
BCCH BC Children's Hospital Vancouver, BC	Siemens Avanto 1.5T	1	0
CHOP Children's Hospital of Philadelphia, PA	Siemens Trio 3T	11	0
	Total	39	64

[1] LRE: Localization Related Epilepsy ; [2] HC: Healthy Controls

Each subject was asked to perform an ADDT test. Typically ADDT is a good probe to identify activations in the superior temporal sulcus but it also activates IFG & MFG [14]. Control subjects were required to be free of any current or past neurological or psychiatric disease. Procedures were performed in accordance with local institutional review board requirements and all subjects gave written informed consent.

B. Data Processing

Different hospitals provided the fMRI datasets and the anatomical MRI using different views and different slicing, voxel size, and resolution. Consequently, we have developed a set of scripts in MATLAB that will apply a rotation matrix to rotate the axis of the fMRI and their views and save the datasets with new settings. fMRI Software Library (FSL) was used to perform the pre and post-processing required to obtaining the images with the resulting activation patterns [21-24].

The operations performed on the datasets were:

1. Preprocessing (motion correction, rotational and translational alignments; filtering and smoothing) aligns all in time series.
2. Statistical model planning for ADDT.
3. Statistical mapping generation.
4. Rendering results co-registered to native and standard spaces.
5. Calculating LI using traditional approach based on (1) and (2) and comparing activation map results obtained at different P-values.
6. Comparing the LI computed for the native and standard space using Excel adding for data analysis tool: "F–test Two-Sample for Variances".
7. Calculating LI for each dataset with a MATLAB script using technique #1.
8. Apply the t-test to LI results on HC and LRE groups.
9. Apply the ANOVA test to the LI results
10. Estimate the LIs for Broca's and Wernicke's areas for the corresponding BA.

All the images used were Z (Gaussianised T/F) statistic images that were thresholded using clusters determined by Z>2.3 and a corrected cluster significance threshold of P=0.05. Only for the first experiment, 3 different P-values were used (0.1, 0.05 and 0.01), whereas for the remaining experiments, a P-value of 0.05 was used to calculate the activation maps. This decision was taken since most of the clinical analyses of brain activation are performed on datasets processed with a P-value of 0.05.

C. Data Collection

To generate a LI which is less affected by these factors, at least 2 basic equations have been introduced. The first computation is a simple counting of active voxels:

$$LI_1 = \frac{CAP_{left} - CAP_{right}}{CAP_{left} + CAP_{right}} \tag{1}$$

where CAP_{left} and CAP_{right} are the counting of the activation points found on the left and right hemisphere of the brain, respectively. This is also known as the *extent of the activation*. Another alternative for computing the LI is given in (2):

$$LI_2 = \frac{\sum_{i=1}^{Xmed} AV_i - \sum_{Xmed+1}^{X\max} AV_i}{\sum_{i=1}^{Xmed} AV_i + \sum_{Xmed+1}^{X\max} AV_i} \qquad (2)$$

Where the summation terms $\sum_{i=1}^{Xmed} AV_i$ and $\sum_{Xmed+1}^{X\max} AV_i$ are the summation of the statistical Z-values of the activation points found on the left and right hemisphere of the brain, respectively. Term *Xmax* refers to the maximum resolution on the *x* axis and *Xmed* is the point corresponding to the alignment of anterior and posterior commissure points. It is assumed that the localization of *Xmed* is made during the activation pattern generation process. This equation deals with the *intensity of the activation* observed.

In order to attenuate the aforementioned drawbacks experienced through the separate implementation of either (1) or (2), both equations are combined to compute the LI$_a$ as shown in (3).

$$LI_a = \frac{LI_1 + LI_2}{2} \qquad (3)$$

Two approaches were used to classify the subjects.

Technique #1: This technique, which uses the bootstrap concept [16], focuses on the canonical language network area as a whole. A mask is applied to the set of activation being processed. Each of the masked slices of the dataset is processed, for each slice an activation subset is defined using a fraction of the activation population of size *n*, for each subset the LI is calculated on a loop of *r* cycles; and the average LI obtained is saved. Finally an average LI is stored. During the processing of each slice, the voxels used for calculation are chosen randomly from a subset of size one third of the identified activation population per subject. The LI so obtained is supposed to be Gaussian distributed. The final LI per slice is averaged among all the meaningful slices, that is, the slices that present a non zero LI, to obtain the final LI for the entire language network area. Each dataset is analyzed based on this computed final LI value.

Technique #2: This is similar to technique #1, except that each dataset is now masked with a specific BA mask. So a given dataset is processed to obtain an individual LI for each BA. The averaged value of BAs 21, 22 and 39 is used to calculate the LI for Broca's area; similarly the averaged LI from BAs 44,45 and 47 was used to calculate LI for Wernicke's area. Each dataset is consequently analyzed based on these two computed LI values.

III. RESULTS

A. Experiment 1

To illustrate the comparison between the LI computed using voxel counting as in (1) and the LI computed using activation intensity summation as in (2), different *P*-values and subject BCCH-001 was selected as illustrative examples to highlight the differences between the two LIs. Three different thresholding values were used at 3 different significance *P*-values (0.1, 0.05 and 0.01). Figs. 1, 2 and 3 show the activation maps that were obtained. BCCH-01 has a 3D volume of 36 slices, each of them of size 64x64 voxels.

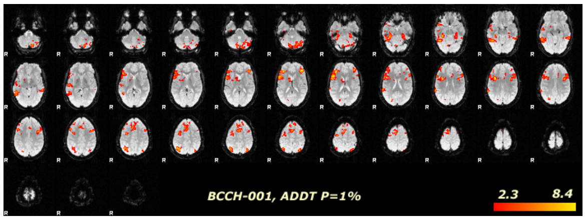

Figure 1. Activation pattern map obtained from subject BCCH-001 using p=1% (11 clusters)

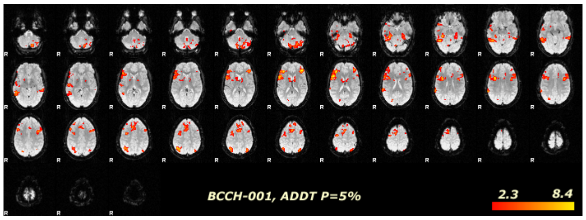

Figure 2. Activation pattern map obtained from subject BCCH-001 using p=5% (13 clusters).

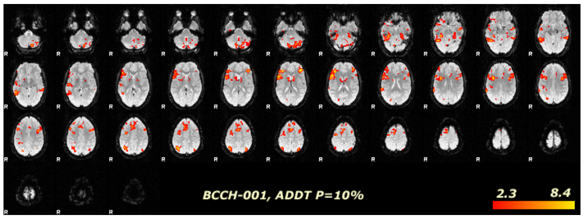

Figure 3. Activation pattern map obtained from subject BCCH-001 using p=10% (16 clusters).

The results in Table II show the LI obtained using voxel counting, activation summation and their average at different P-values in native space for subject BCCH-001.

The NMI 3 mm normal brain was used on all the 114 datasets. A P-value of 5% was used for the rest of the experiments, as it is a value most commonly accepted by the medical community.

The control group yielded a mean LI of 0.55107 with a standard deviation of 0.3827 and standard error mean of 0.047, while the LRE group yielded a mean LI of 0.2751 with a standard deviation of 0.7486 and a standard error mean of 9.1198.

Application of the *t*-test to the control and normal groups resulted in a t-value of 2.471 and a P-value of 0.0151, which indicates a statistically significant difference in the mean of both groups. The LI was also calculated using both native and normal spaces for each subject; however, no statistically significant difference between the two spaces was found in this case.

TABLE II. LI VARIATION DUE TO DIFFERENT THRESHOLDING IN THE NATIVE SPACE APPLIED TO SUBJECT BCCH-001

LI(1) Counting Voxels	LI(2) Summing Activations	(3) Final LI	Dif. LI(1) - LI(2)	P-Value
-0.2273	-0.2415	-0.2344	-0.0142	0.10
-0.2251	-0.2428	-0.23395	-0.0177	0.05
-0.2220	-0.2362	-0.2291	-0.0142	0.01

Using the single-factor ANOVA, statistical significance was tested by comparing the F-value, which is defined in (4).

$$F = \frac{\sigma_{\mu_{\text{inter}}}}{\mu_{\sigma_{\text{intra}}}} \quad (4)$$

Where $\sigma_{\mu_{\text{inter}}}$ is the variance of the inter-group means, while $\mu_{\sigma_{\text{intra}}}$ is the mean of the intra-group variances.

The results, displayed in Fig. 4, showed a small variation between the LI obtained using native space and the LI computed using standard space. However, a statistical analysis was performed on the two independent groups. For the control group, an F-score of 1.089 was obtained during the ANOVA test, while the critical F-value suggested by the Excel data analysis was 3.9163, which support our original statement. On the other hand, for the LRE subjects, an F-score of 0.1915 was obtained during the ANOVA test, while the critical F-value suggested was 3.9667, which concludes no statistical difference between the LI calculated on standard and native space.

B. *Experiment 2*

The same datasets as in Experiment 1 were used in this second experiment.

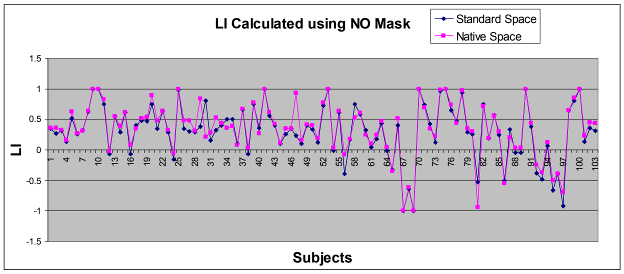

Figure 4. LI calculated using (3) for all subjects using standard and native space with NO Mask

This experiment evaluates the merits of using Technique 1 described earlier. Table III shows the LI obtained using masks for the language network regions (Broca's and Wernicke's areas) on both the native and standard spaces. In this case, the NMI 3 mm normal brain was also used. A P-value of 5% was used for post-processing all activation maps. Based on the computed LI using Technique 1, subjects were classified as strong lateralized (|LI|≥0.5), lateralized (0.2≥|AI|<0.5) and bilateral (|LI|<0.2). The results are as shown in Table III.

TABLE III. DISTRIBUTION OF SUBJECTS BASED ON LI CALCULATED USING BROCA'S AND WERNICKE'S AREAS.

Region	Control group: 64		LRE Group : 39	
	Nr.	*%*	*Nr.*	*%*
Strong Right LI	0	0	7	17.9
Right LI	0	0	4	10.3
Bilateral	9	14	4	10.3
Left LI	12	19	2	5.1
Strong Left LI	43	67	22	56.4

From the spatial distribution of the population shown in Fig. 5, it is not possible to separate control from LRE subjects since significant overlap exist between them. However, it provides a better understanding of the activation pattern display by each subject. It clearly shows 26% (10/39) of the LRE subjects with right activation in both, temporal and frontal areas. This distribution also helps in identifying unilateral left/right activation in the frontal and/or temporal area when $LI = \pm 1$, as well as a combination of unilateral and bilateral activation patterns for temporal and frontal regions.

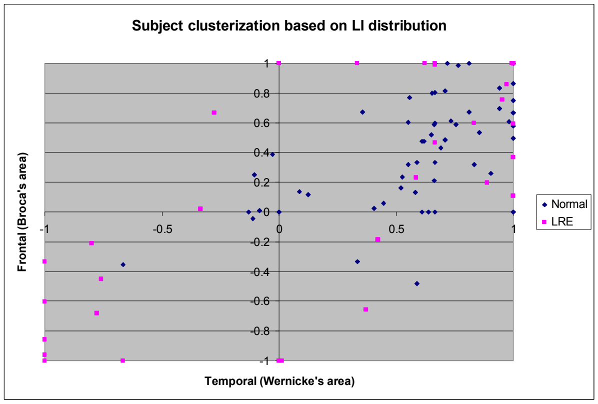

Figure 5. Distribution of the population based on the spatial relation between the LI coefficients calculated for Broca's and Wernicke's areas.

C. *Experiment 3*

Brain cortex has a standard accepted division in areas called Brodmann Areas. There are 52 original areas [25], however in this study the LI computation was performed for the first 48 areas only.

Table IV indicates the main functions associated to each of these areas. In Fig. 6 the BA location and their associated functionality are shown as described by B. Kolb [25]. The reader can note how Broca's and Wernicke's areas are associated to 3 BAs each.

TABLE IV. BRAIN FUNCTIONS ASSOCIATED TO THE BRODMANN AREAS

Function		**Brodmann Area**
Vision	Primary Secondary	17 18,19,20,21,37
Auditory	Primary Secondary	41 22,42
Body senses	Primary Secondary	1,2,3 5,7
Sensory, Tertiary		7,22,37,39,49
Motor	Primary Secondary Eye Movement Speech	4 6 8 44
Motor Tertiary		9,10,11,45,46,47

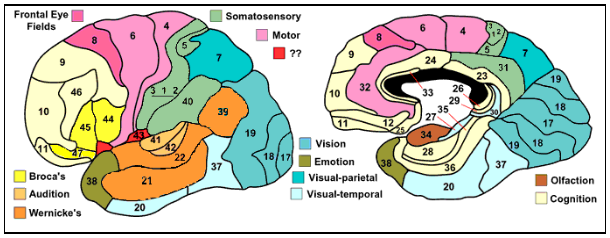

Figure 6. BAs of the brain cortex and their relation to main known brain functions.

ANOVA test was performed on the LI obtained in an effort to investigate the behavior of the BA across control and LRE subjects. We also applied the ANOVA test to evaluate the behavior of each subject across the 48 BAs.

For the ADDT paradigm, we identified 2 BAs which never undergo any activation: 12 and 33, since areas 13, 14, 15, 16 and 31 are non existent for the human brain, they were considered only for monkey brains. In order to assess the participation Standard deviation (σ), average (μ) and Signal to Noise Ratio (SNR=μ/σ) for each BA were also calculated. The criteria to select the BA more significantly involved in the ADDT task were to select the BAs which yielded more SNR in the experiment. Our results showed the 10 BA's more significant for ADDT activation were 21, 22, 41, 42, 6, 48, 45, 44, 39, and 37. As explained before, BA 21, 22, and 39 are the so called Wernicke's area, while 45 and 44 belong to the Broca's area. However BA 47 which is also considered as part of Broca's area was not found to be on the 10 more significant BAs. BA 41 and 42 are related to primary and secondary auditory functions, while area 6 is secondary motor functions, and BA 37 relates to sensory functions.

After calculating the LI for each of the BAs for each subject, we observed a surface as shown in Fig. 7. Recall that subjects 1 through 64 are used as the control group and subjects 65 to 103 are used as the LRE group. From Fig. 7, a pattern can be identified to associate subjects based on the LI ranges obtained on their activation.

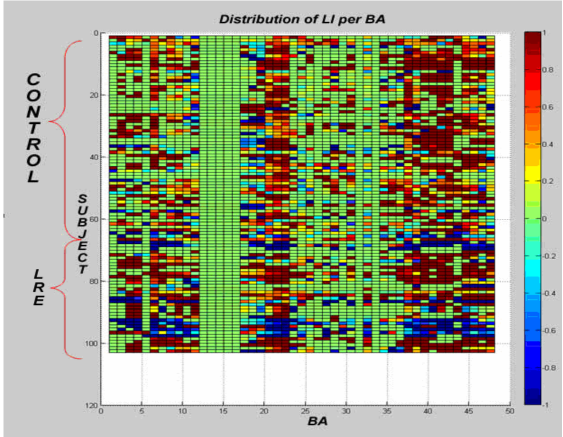

Figure 7. Top view of LI surfaced obtained for each BA on 103 subjects.

As can be observed from Fig. 8, a decreased language lateralization in LRE subjects is present, especially in the frontal cortex, because of a more bilateral activation of the Broca's area compared with primarily left hemisphere activation in the control group. Interestingly, a similar behavior was found on a study involving subjects having different brain pathologies such as schizophrenia, where it was also observed that decreased lateralization was correlated to the severity of hallucinations on schizophrenia and dementia [26]. The intensity values in the activation maps were also analyzed. The intensities averages for language areas of the brain are displayed in Table V. These results show that the LRE population tends to have higher intensities in their activation maps.

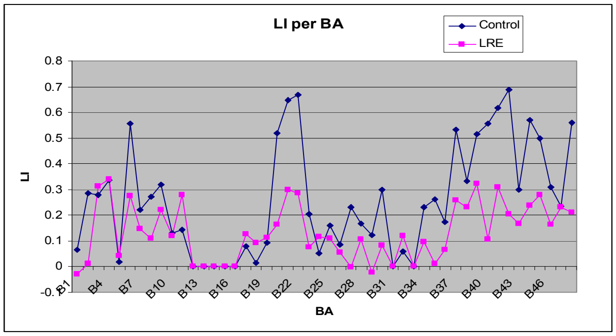

Figure 8. Average LI per BA for control and LRE groups

TABLE V. DISTRIBUTION OF AVERAGE INTENSITIES IN BROCA'S AND WERNICKES' ACTIVATION AREAS FOR CONTROL AND LRE GROUPS.

Region	**Laterality**	**Average Intensity for Group**	
		Control	***LRE***
Broca's Area	L	500.9	625.2
	R	209.1	470.6
Wernicke's Area	L	614.3	436.8
	R	151.3	239.8

IV. CONCLUSIONS

This study have explored different ways of computing the LI in normal and LRE patients and proved that the traditional use of standard and native spaces does not lead to significant differences in the computed LI as can be concluded from the results of Experiment 1. Specifically, the trend for the computed value of LI per each BA observed indicates that the LI values for the LRE group are lower as compared to control data. Moreover, differences in activation patterns of control and LRE groups are found as evidenced by the results of Experiment 2.

As for Experiment 3, the results indicate a decreasing trend of left activation and the development of bilateral activation or left activation in some cases.

With these experimental results, the main findings can be summarized as follows:

1. LI variability due to difference in space (native vs. standard) is not significant.
2. LI variability due to epilepsy in the population studied is statistically significant.
3. The trend observed for the LI per BA indicates that the values are reduced as compared to control data. This indicates a decreasing trend of left activation and the development of bilateral activation or left activation in some cases. This finding is consistent with lateralization studies on other brain pathologies.
4. Using multiple LIs for specific brain areas, spatial information can be added to the merit of lateralization, obtaining additional spatial information that a single LI value cannot convey.
5. It was possible to identify the top 10 BAs affected by the ADDT as result of our experiments. These areas are BA 21,22,41,42,6,48,45,44,39, and 37. This result is consistent with the expected language network areas (Broca's and Wernicke's areas), but also present considerable activation on other areas of the brain indirectly connected to language tasks such as auditory and motor areas. Furthermore, activation associated to other language network paradigms such as auditory category task (ACT), listening task (LST), verbal fluency (VF), and reading task may complement or augment aforementioned findings.

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