

# Evaluation of Hippocampal Function in Temporal Lobe Epilepsy: Spatial Bayesian Variable Selection and Grouping the Regression Coefficient in Multilevel Functional Magnetic Resonance Imaging Data Analysis

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Received: 14 December 2019

Revised: 09 February 2020

Accepted: 19 February 2020

## What's Known

- The limitations of the usual brain analysis model were resolved by the spatial Bayesian variable selection (SBVS) method. A regression model that simultaneously considers SBVS and the grouping of brain voxels is termed the "Ising and Dirichlet Process (Ising-DP)".

## What's New

- Ising-DP model appropriately detected active voxels in the hippocampal area with little evidence of false-positives in other areas.
- Ising-DP model, adjusted for between-subject factors, reduced shadow and false-positive areas, indicating a better fit of the model.

## Abstract

**Background:** A pre-surgical evaluation of cognitive functions in patients with mesial temporal lobe epilepsy (mTLE) is critical. The limitations of the usual brain analysis model were resolved by the spatial Bayesian variable selection (SBVS) method. An Ising and Dirichlet Process (Ising-DP) model considers SBVS and the grouping of a large number of voxels. The present study aimed to identify brain areas involved in episodic memory in patients with right mTLE and controls via the Ising-DP model. The model was extended to include between-subject factors (BSFs), and the results were compared with other classical methods.

**Methods:** The present cross-sectional study was conducted on 15 patients with right mTLE and 20 controls in Tehran, Iran, in 2018. During functional magnetic resonance imaging, the subjects were tested with the face-encoding memory task, followed by a recognition memory test. The participants demographic factors such as age, sex, marital status, area of residence, and years of schooling were considered to comprise BSFs. The independent  $t$  test, the chi-square test, and the correlation test were conducted using the SPSS software (version 20.0). The image processing was carried out using SPM (version 12.0) and MATLAB (version R2014a).

**Results:** The Ising-DP model appropriately ( $R^2=0.642$ ) detected activated hippocampal areas. The model adjusted for BSFs indicated a better fit by the significant effect of age ( $P[\gamma]>0.91$ ), sex ( $P[\gamma]>0.87$ ), and years of schooling ( $P[\gamma]>0.89$ ). The heat maps exhibited decreased activation in the right hippocampal region in the patients compared with the controls ( $P<0.0001$ ). Right hippocampal activity had a significant positive correlation with the recognition memory test in the mTLE group ( $r=0.665$ ) and the control group ( $r=0.593$ ).

**Conclusion:** The Ising-DP model was sufficiently sensitive to detect activated areas in our patients with right mTLE during the face-encoding memory task. Since the model adjusted for BSFs improved sensitivity, we recommend the use of more detailed BSFs such as seizure history in future research.

Please cite this article as: Zare R, Saberi H, Parsaeian M, Rahimiforushani A. Evaluation of Hippocampal Function in Temporal Lobe Epilepsy: Spatial Bayesian Variable Selection and Grouping the Regression Coefficient in Multilevel Functional Magnetic Resonance Imaging Data Analysis. Iran J Med Sci. 2021;46(3):189-197. doi: 10.30476/ijms.2020.84478.1429.

**Keywords** • Bayes theorem • Magnetic resonance imaging • Hippocampus • Epilepsy, temporal lobe

## Introduction

Mesial temporal lobe epilepsy (mTLE) is a chronic disorder of the nervous system with a pathophysiological basis, namely hippocampal sclerosis.<sup>1</sup> There is evidence from both human and animal investigations, which indicated mTLE affects psychological capacities, particularly episodic memory.<sup>2</sup> Episodic memory is a type of long-term memory that serves as the collection of past personal experiences having occurred at a certain time and place. The surgical resection of the affected hippocampal area carries a 60% to 70% chance of seizure control,<sup>3</sup> but it has cognitive risks, particularly for memory, if the image of the lesion area fails to show the exact location.<sup>4</sup> Verbal and visual memories may be active in the left and right hippocampal regions, respectively.<sup>5</sup> Thus, a pre-surgical evaluation of cognitive functions such as memory in the case of temporal lobectomy in patients with refractory mTLE is critical.

Functional magnetic resonance imaging (fMRI) has gained acceptance as a promising, noninvasive, and reproducible pre-surgical evaluation method with a high spatial resolution for imaging regional brain functions. fMRI uses endogenous blood-oxygen-level-dependent (BOLD) contrast to visualize task-specific changes in the regional cerebral blood flow and metabolism. The detection of brain activity is usually achieved based on a voxelwise regression model termed “statistical parametric mapping (SPM)”.<sup>6</sup> This approach relies on the parametric general linear model and calculates the *t*-value for each voxel within a slice. SPM has such limitations as multiple-comparison problems, caused by large numbers of voxels, and conservative Bonferroni correction results. Some limitations also arise because SPM is based on classical inference procedures.<sup>7</sup>

The recent years have witnessed the introduction of a new approach, which utilizes a spatial Bayesian variable selection (SBVS) method,<sup>8, 9</sup> whereby, for each voxel, the latent binary activation indicator explicitly parameterizes whether the voxel is active or inactive. The most important advantage of this approach is that it focuses on the estimation of activation probabilities, not activation amplitudes.

Smith and colleagues introduced an Ising prior to the SBVS model for a set of binary indicator variables.<sup>8</sup> Improvement in edge preservation for the spatial smoothing of activation areas is one of the advantages of this prior. The external field of the Ising prior takes into account any prior knowledge of the likely areas of activation. Given that the sample size is

smaller than the number of indicator variables, it is desirable to group the indicator variables so that regression coefficients with similar values can be congregated. A regression model that simultaneously considers an Ising prior for spatial correlation and the grouping of brain voxels is termed the “Ising and Dirichlet Process (Ising-DP)”.<sup>10</sup>

In the present study, we aimed to identify brain areas involved in episodic memory processing in patients with right mTLE and the normal controls via the Ising-DP model. Between-subject differences prompted us to extend the model to include between-subject factors (BSFs). Moreover, we sought to ascertain whether this model would provide concordant results with other classic methods such as SPM.<sup>11</sup>

## Patients and Methods

### Participants

This cross-sectional study was carried out in the Neuroimaging Center of Imam Khomeini Hospital, affiliated with Tehran University of Medical Sciences, Tehran, Iran, in 2018. The research protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (Code: IR.TUMS.SPH.REC.1396.3979). The participants were 35 right-handed adults. As the experimental unit in brain image analyses is voxels, and one person might have about 150 000 or more voxels, the actual sample size in this study was about five 250 000 units. Fifteen patients suffering from mTLE with right hippocampal sclerosis (the experimental group), and 20 normal subjects with no psychiatric and neurological illnesses (the control group) were selected via the convenience sampling method. The exclusion criteria consisted of other neurological illnesses, psychiatric disorders, active medical diseases, and unwillingness to participate in the study. The normal subjects, chosen for the control group, were within the age range of the patients. The healthy status of the control group was confirmed by a neurologist. None of the participants in the control group was on psychotropic medications. A written informed consent form was completed by all the participants.

### Study Protocol

The nonverbal face-encoding memory task was employed in this study. It incorporated 60 unfamiliar human faces selected from the Yale Face Database and the PICS Database.<sup>12</sup> Samples of the human faces are presented in figure 1. During fMRI, six faces were presented in 10 blocks, which were started in the rest



**Figure 1:** Samples of the stimuli presented to the subjects during the encoding condition are shown herein.

state (figure 2). Before fMRI, the subjects were instructed to remember the faces for a later test. The recognition memory test, comprised of 30 new faces and the 60 faces presented during fMRI, was done approximately 20 minutes after scanning. During the test, the subjects were asked whether the pictures were new or identical to the one previously shown. Two states were assumed for the 60 target faces: a subject can recall faces (R response) or not (F response).

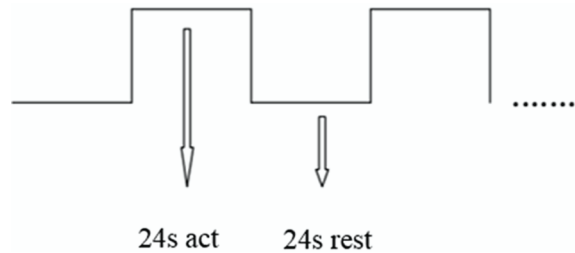
#### *Magnetic Resonance Imaging Acquisition*

Images were acquired on a Siemens 3 T Trio scanner with a 12-channel head coil. Functional T2\*-weighted images were collected with an echo time (TE) of 30 ms, repetition time (TR) of 3000 ms, field of view (FOV) of 192 mm<sup>2</sup>, flip angle of 90°, voxel size of 3×3×3 mm<sup>3</sup>, matrix size of 64×64, slice gap of 0 mm, and slice thickness of 3 mm.

#### *Statistical Analysis*

BSFs were compared between the study groups through the use of the independent *t* test for the continuous variables, and the chi-square/Fisher exact test for the categorical variables. The association between the number of activated voxels in the right hippocampal region and the number of hits in the recognition memory test was checked using a correlation test. The BSF analysis and the correlation test were done using IBM SPSS, version 20. A probability of less than 0.05 was considered statistically significant.

Pre-statistical processing and single-subject analyses were performed using the SPM12 software (version 12.0, London, UK). First, the



**Figure 2:** Schematic diagram of the experimental design in the present study is illustrated.

slice-timing of the images was corrected, and the images were realigned (motion corrected). Afterwards, they were normalized to a template in the Montreal Neurological Institute and Hospital (MNI) standard.<sup>13</sup> Finally, spatial smoothing with a Gaussian kernel of full-width half-maximum (FWHM) of 5.0 mm was used to smooth the images. Trial-specific responses were modeled by convolving a delta function with the canonical hemodynamic response function.

In the first-level analysis, a voxelwise regression was employed to obtain the contrast signals for all the voxels of each subject corresponding to the memory effect. In this regression, the hemodynamic response function was considered to be the response variable, and a dummy variable was utilized to define the act or rest period. Contrast signals were obtained based on the beta coefficients (act minus rest) of the models. For the second-level analysis, a model was defined as follows:

$$Y = X\eta + \varepsilon$$

where  $Y$  ( $n \times 1$ ) was the response variable in the recognition memory test score, and  $X = (X_1, \dots, X_p)$  was the  $n \times p$  matrix of the covariates. The

covariates comprised contrast signals, which were obtained from the first-level analysis, and/or BSFs, which were considered to be age, sex, marital status, area of residence, and years of schooling. The error term ( $\epsilon$ ) was assumed to have an  $N(0, \sigma^2 I_\eta)$  distribution.<sup>10</sup>

The SBVS approach was employed to indicate which covariates were included in the model. In this approach, for each voxel, a latent indicator ( $\gamma_i$ ) was defined to select the voxels, that were significantly predictive of the response. An Ising prior was imposed on the latent binary indicators to incorporate the spatial information between the voxels, and, in parallel, a DP prior was imposed on  $\eta$  to achieve the grouping of the regression coefficients.<sup>10</sup>

The posterior inference of the proposed models was conducted using a Gibbs sampler with data augmentation. For each model, 8000 iterations of the Markov chain Monte Carlo (MCMC) were performed, with the first 1000 discarded as burn-ins. The convergent property was assessed by trace plots. For the calculation of the posterior inclusion probabilities  $P(\gamma_i=1|Y)$ , the number of iterations, where  $\gamma_i$  was equal to 1, was divided by the total number of iterations excluding the burn-in period. The number of activated voxels based on SPM was counted by considering the critical value for  $P(\gamma_i=1|Y)$  to be 0.8772.<sup>8</sup>

The second-level analysis was done using the MATLAB software (version R2014a, USA). The MATLAB code of the Ising-DP model for the second-level analysis, which was written by Li and colleagues, is available.<sup>10</sup> For the use of the first-level output (i.e., contrast signals as an input of this code), its nifti (.nii) format was converted into the text (.txt) using the *fs/2sacii* command of the FSL software (version: 5.0.6, Germany).

## Results

The participants were 35 right-handed adults: 15 patients with right mTLE at a mean age of  $25.46 \pm 5.38$  years, and 20 normal controls at a mean age of  $26.71 \pm 6.12$  years. There was a significant difference between the mean years of schooling ( $P=0.032$ ), and the area of residency ( $P=0.040$ ) between the mTLE and control groups. The proportions of females, unmarried individuals, and urban residents were higher in both mTLE and control groups. The posterior inclusion probabilities of the latent indicator ( $\gamma$ ) of age, sex, and years of schooling exceeded the critical value of 0.8772 (table 1).

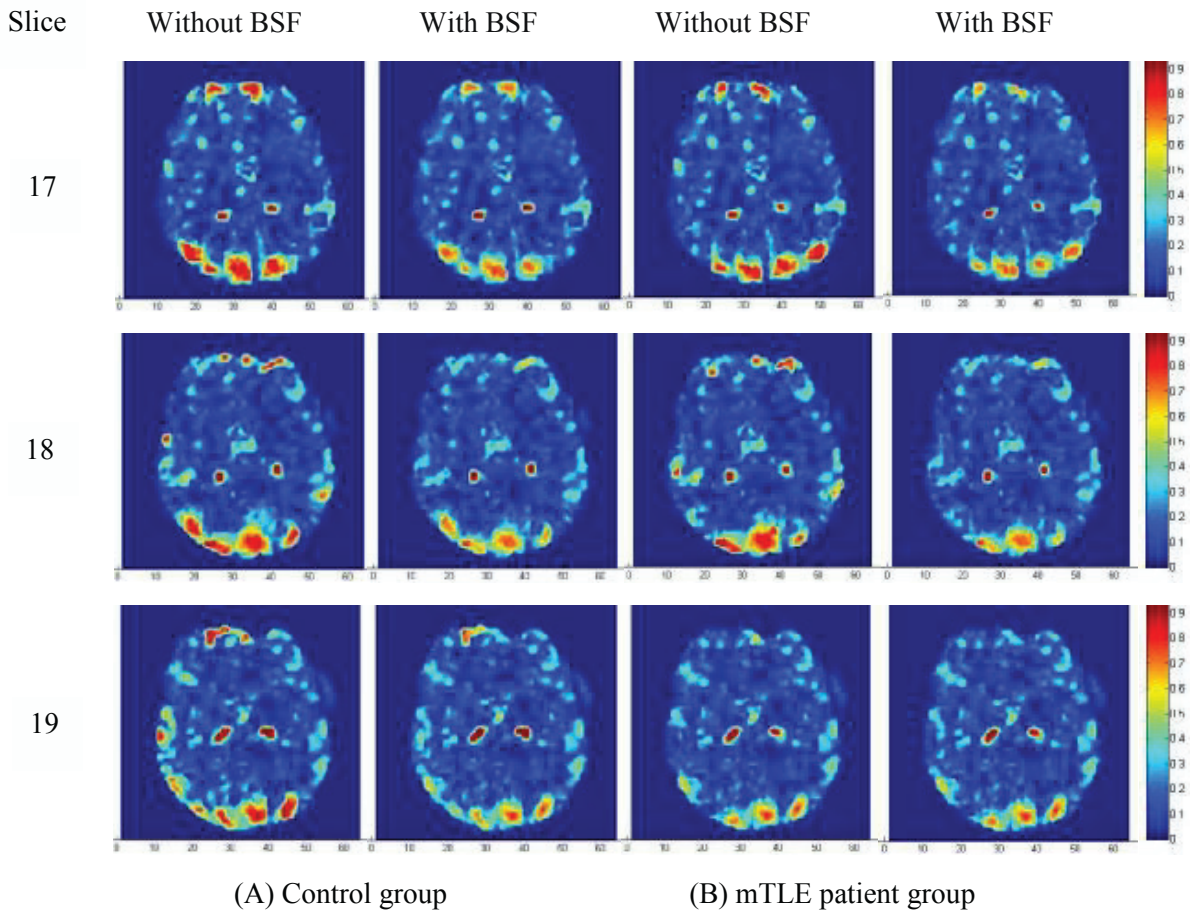
The fMRI image processing was restricted to all voxels lying within three slices close to the hippocampal region in all the participants. Figure 3 depicts the heat maps of the posterior selection probabilities of the voxels, achieved by the Ising-DP model with and without BSFs among the control (Part-A), and mTLE (Part-B) groups. (The color scale is arbitrary, with dark blue representing the probability of activation to be zero and dark red representing the probability of activation to be 1.) In figure 3, there are two dark red areas ( $P[\gamma_i=1|Y] \geq 0.8772$ ) within the slices representing the hippocampal area. The small and scattered areas with the dark red color exhibit false-positive activation. The heat maps are drawn for all the voxels in each slice without considering the critical value of 0.8772. Therefore, the light red areas at the top and bottom of the heat maps represent high posterior inclusion probabilities in the prefrontal and occipital cortices.

The Ising-DP model with an R-square value ( $R^2$ ) of 0.642 detected clear activation for the hippocampal area with little evidence of

**Table 1:** Between-subject factor distributions in the 15 patients with mesial temporal lobe epilepsy and the 20 controls

BSF	Total (N=35)	Patient Group (n=15)		Control Group (n=20)		P value
	Mean±SD	Mean±SD	P ( $\gamma$ )	Mean±SD	P ( $\gamma$ )	
Age (years)	26.21±5.59	25.46±5.38	0.911	26.71±6.12	0.932	0.468 <sup>a</sup>
Years of schooling	15.13±2.29	14.10±2.29	0.984	15.80±2.14	0.912	0.032 <sup>a</sup>
	N (%)	N (%)	P ( $\gamma$ )	N (%)	P ( $\gamma$ )	
Sex						
Female	13 (37.14)	6 (40)	0.903	7 (35)	0.875	0.762 <sup>b</sup>
Male	22 (62.86)	9 (60)		13 (65)		
Marital status						
Unmarried	22 (62.86)	10 (66.67)	0.466	12 (60)	0.542	0.686 <sup>b</sup>
Married	13 (37.14)	5 (33.33)		8 (40)		
Area of residence						
Urban	25 (71.43)	8 (53.33)	0.343	17 (85)	0.291	0.040 <sup>c</sup>
Rural	10 (28.57)	7 (46.67)		3 (15)		

BSF: Between-subject factor; <sup>a</sup>Independent *t* test; <sup>b</sup>Chi-square test; <sup>c</sup>Fisher exact test;  $\gamma$  is the latent indicator of the Ising-DP model; P( $\gamma$ ) is the posterior inclusion probability



**Figure 3:** Figure illustrates the heat maps of three slices of the brain, which included the hippocampal area, according to the ranks of their posterior inclusion probabilities obtained from the Ising-DP model, with and without between-subject factors: (A) the control group (n=15) and (B) the mTLE patient group (n=15). Ising-DP: Ising and Dirichlet Process; mTLE: Mesial temporal lobe epilepsy

false-positives. The edge-preserving property of the external field in the Ising prior identified the areas of activation with small shadow. These two properties, namely the preservation of the anatomical structure and the detection of the area with small shadow, indicate the sensitivity of the model. Adjustments of the model for BSFs reduced the posterior inclusion probability for many of the voxels, especially the nonactivated ones. Therefore, the adjusted model diminished shadow, and some false-positive areas with a high posterior inclusion probability (figure 3). The pattern of activations with and without BSFs in the mTLE group was the same as that of the control group. The exception was that the experimental group exhibited decreased activation in the right hippocampal region in contrast to the control group.

The number of activated voxels in the right hippocampal region ( $P[Y_i=1|Y] \geq 0.8772$ ) with and without BSFs for both groups is presented in table 2. After adjustments for BSFs, the number of activated voxels in each slice was declined in both patient and control groups; the difference, however, was not statistically significant. The

number of activated voxels was significantly lower in the mTLE group than in the control group ( $P < 0.0001$ ) (table 2).

The results of the single analysis of activation intensity in the right hippocampal region, the results of the recognition memory test in each patient in the mTLE group, and the control group are presented in table 3. By comparison with the healthy controls, the patients with right mTLE demonstrated reduced activation intensity and activated voxels in the right hippocampal region. The mean number of hits in the experimental group was lower than that in the control group. Furthermore, the mean number of false-positives in the patient group was higher than the control group. The correlation between the number of activated voxels and the number of hits in the recognition memory test was statistically significant in the control group ( $r=0.593$ ,  $P=0.025$ ), and the mTLE group ( $r=0.665$ ,  $P=0.007$ ).

## Discussion

We used a recent statistical fMRI data analysis

**Table 2:** Number (%) of activated voxels in the right hippocampal region with and without between-subject factors in the patients with mesial temporal lobe epilepsy and the control group

Slice	Patient Group (n=15)	Control Group (n=20)	P value
Slice 17			
Without BSF	128 (5.56)	287 (12.48)	<0.0001
With BSF	111 (4.83)	266 (11.57)	<0.0001
P value	0.259	0.341	-
Slice 18			
Without BSF	141 (6.13)	273 (11.87)	<0.0001
With BSF	129 (5.61)	246 (10.70)	<0.0001
P value	0.452	0.208	-
Slice 19			
Without BSF	135 (5.87)	270 (11.74)	<0.0001
With BSF	118 (5.13)	258 (11.22)	<0.0001
P value	0.272	0.579	-

Activated voxels were determined according to the critical value of 0.8772. All the P values were calculated by the chi-square test. BSF: Between-subject factor

**Table 3:** Activation intensity in the right hippocampal region and the result of the recognition memory test in each patient and the control group

	Activated Voxels (N)	Mean±SD	Hit (N)	FP (N)
Normal Group	1364	11.25±12.36	44	2
Patient 1	481	3.11±13.31	31	9
Patient 2	408	2.46±16.29	27	14
Patient 3	386	2.12±11.51	29	10
Patient 4	394	3.02±19.76	30	10
Patient 5	474	2.68±17.36	31	9
Patient 6	368	3.20±18.21	26	8
Patient 7	399	3.05±11.26	35	9
Patient 8	412	2.65±15.34	38	11
Patient 9	491	2.23±17.55	31	12
Patient 10	477	3.15±13.85	30	11
Patient 11	426	2.52±14.69	29	9
Patient 12	354	2.21±12.85	25	10
Patient 13	386	2.79±16.24	24	14
Patient 14	492	2.95±14.63	35	7
Patient 15	463	3.26±11.46	38	9

N: Number; FP: False-positive

method to detect hippocampal activation by episodic memory encoding in patients with right mTLE and normal controls. In this method, spatial correlation is directly modeled for activation probabilities themselves. There is also no need for the spatial post-processing step, because the posterior distribution takes into account the spatial structure of the Ising prior. Another extremely useful property of this method is the ability to use prior information about the likely areas of activation in the external field of the Ising prior. This can include anatomical data such as the distribution of the gray matter.

To avoid the posterior computational burden, and to speed up model fitting, we grouped large numbers of regression coefficients with similar effects into a small set of values via the DP prior. Due to the clustering effect of the DP prior, there

were fewer than 10 regression coefficient values in most of the iterations.

Our results showed the Ising-DP model had the goodness of fit as well as a good detection sensitivity. In both experimental and control groups, the edge-preserving property of the Ising prior identified small and clear areas of activation. These findings are concordant with previous fMRI studies, even though those investigations used another task and thus, found another activation region.<sup>9, 14</sup>

The distinct advantage of our study was the inclusion of BSFs in the second level of analysis, which considerably improved sensitivity in detecting activated areas, and reduced false-positive activation. On account of studies that have shown a statistical relationship between sex,<sup>15</sup> age,<sup>16</sup> and years of schooling,<sup>17</sup> and several

aspects of hippocampal performance, it seems desirable to assess hippocampal activity by adjusting the models for BSFs. The results of the model exhibited decreased activation in the right hippocampal region of our patients with the right mTLE compared with our control group. This finding is in the same line with the SPM result reported by Gholami and colleagues.<sup>11</sup> The most striking pattern identified by the Ising-DP model was that the areas with the highest selection probabilities were smoothly located across the hippocampal regions. This finding is in line with a study by Li and colleagues, who introduced and proposed this model, and showed that the Ising-DP prior inherently assumed sparsity.<sup>10</sup> Otherwise speaking, only a small portion of the voxels was associated with the individual scalar outcome in their investigation. All of our findings are similar to their results.

In our study, the mTLE group was less successful than the control group in the recognition memory test, which is in agreement with a previous study that used a visual confrontation naming test. That investigation showed that patients with both right and left TLEs had significantly lower naming scores than controls, patients with right TLE performed better than those with left TLE, and left hippocampal activation during the verbal fluency task had a significant positive correlation with naming scores in controls, and patients with the right (but not left) TLE.<sup>18</sup> These findings are in agreement with our study, which showed that right hippocampal activity had a significant positive correlation with the recognition memory test in both right mTLE and control groups.

To our knowledge, there is a limited number of studies on the detection of hippocampal activity by episodic memory encoding,<sup>19,20</sup> and there is no study even regarding other memory hierarchies adjusted for BSFs.<sup>21</sup> A remarkable point in our study is that we applied our proposed model by adjusting it for BSFs to detect hippocampal activity by episodic memory encoding.

To identify activated brain areas, most fMRI studies on patients with mTLE have focused on activity regions,<sup>22</sup> encoding tasks,<sup>23</sup> and trial designs,<sup>24</sup> while statistical methods appear to be one of the most significant components of any research. In this study, we assessed the results obtained from a recent statistical fMRI data analysis method on the brain. The natural features of the mesial temporal lobe such as its small size and small BOLD response, alongside sclerotic changes in patients with mTLE, render a meticulous selection of the statistical method crucial.

The Markov random field theory can solve

multiple comparison problems in determining the significance threshold in brain image processing. Kalus, Sämann, and Fahrmeir proposed a probit model based on this theory.<sup>14</sup> Although the Ising prior is the spatial case of Markov random field, the probit prior simplifies the calculation of the hyperparameters of the Ising prior. However, the computation of a large-sized voxel matrix by the probit model is hard and time-consuming. It is possible to combine the DP prior to the probit model.

The Ising-DP model appropriately detected activated voxels in the hippocampal area with little evidence of false-positives in other areas. We suggest that future studies analyze fMRI images via the Ising-DP model. Our results could also encourage investigators to apply other recent spatial methods with a view to enhancing the fMRI data analysis. Another distinct aim of the current study was model adjustments for BSFs. The heat maps, which we obtained, exhibited reduced shadow in the hippocampal region, and decreased false-positive areas, indicating a better fit of the model. Hence, further studies should assess more detailed BSFs such as Intelligence Quotient (IQ),<sup>25</sup> race, history of brain diseases in healthy subjects, history of seizure, age at seizure onset, epilepsy duration,<sup>26</sup> and epilepsy severity in patients. Indubitably, a larger sample size would have further bolstered the results of our study.

The findings of the current investigation should be interpreted in light of the following limitations. First and foremost, we did not consider the confounding effects of antiepileptic drugs. Additionally, since the left and right hippocampal regions are activated by different memory-encoding tasks, it was not feasible for us to compare the activation of these two regions. Therefore, future research could focus on verbal and nonverbal memory-encoding tasks simultaneously<sup>5</sup> or imaging patients with TLE in the rest state.<sup>27</sup> Another weakness of note is that we failed to compare structural changes such as the hippocampal volume between patients with mTLE and healthy controls. This deficiency could be addressed in future research through structural analyses on anatomical images. It is worthy of note that we extended the Ising-DP model to a multilevel Ising-DP model to include BSFs as the second level. Finally, our study is restricted to the model application; future investigations should address such other theoretical concepts as model formulation, and Bayesian posterior closed-form expression. Undoubtedly, simulation is needed to determine the validity of the model.

## Conclusion

The Ising-DP model was sufficiently sensitive to detect activated hippocampal areas in our patients suffering from mTLE during the memory-encoding task. The edge-preserving property of the Ising prior identified small and clear areas of activation, and the clustering effect of the DP prior sped up model fitting. Additionally, the inclusion of BSFs augmented sensitivity in detecting activated areas and reduced false-positive activation. The extended model confers the possibility of using more detailed BSFs such as seizure history in future research.

## Acknowledgment

This study was supported by Tehran University of Medical Sciences (TUMS) and was extracted from a PhD thesis by Roghaye Zare. We would like to express our thanks to H. Farrahi for his valuable comments and F. Abazari for English editing.

**Conflict of Interest:** None declared.

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