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Original Article

On The Search for Convergence of Functional Brain Patterns across Neuroimaging Studies: A Coordinate-Based Meta-Analysis Using Gibbs Point Process

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ABSTRACT

Introduction: Coordinate-based meta-analysis (CBMA) is a standard method for integrating brain functional patterns in neuroimaging studies. CBMA aims to identify convergency in activated brain regions across studies using coordinates of the peak activation (foci). Here, we aimed to introduce a new application of the Gibbs models for the meta-regression of the neuroimaging studies.
Methods: We used a dataset acquired from 31 studies by previous work. For each study as well as foci, study features such as SD duration and the average age were extracted. Two widely Gibbs models, Area-interaction and Geyer saturation were fitted on the foci. These models can quantify and test evidence for clusters in foci using an interaction parameter. We included study features in the models to identify their contribution to foci distribution and hence determine sources of the heterogeneity.
Results: Our results revealed that latent study-specific features have a moderate contribution to the heterogeneity of foci distribution. However, the effect of age and SD duration was not significant ($p<0.001$). Additionally, the estimated interaction parameter was 1.34 ($p<0.001$) which denotes strong evidence of clusters in foci.
Conclusion: Overall, this study highlighted the role of the interaction parameter in CBMA. The results of this work suggest that Gibbs models can be considered as a promising tool for neuroimaging meta-analysis.

Introduction

In recent years, numerous functional neuroimaging studies are conducted to capture functional brain patterns in healthy subjects or patients with neurological diseases while doing specific tasks or resting state. Hence, the result of a functional neuroimaging analysis (fMRI, PET, …) is a set of clusters of voxels that are jointly above a certain statistical threshold. For each study, cluster positions are given in terms of three-dimensional coordinates

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in predefined stereotactic spaces (i.e., MNI, Talairach). Conventionally, authors report the coordinates of the cluster's "peak" (foci), or the cluster's geometrical center or its center of mass. The foci pattern often affected by connectivity among functional networks, and its identification becomes more complex when different studies are not conducted under the same condition. Coordinate-based meta-analysis (CBMA) is a standard method for integrating functional brain patterns in neuroimaging studies.[1] The general idea of CBMA is to extract the foci for each study and integrate them into one activation map that captures brain activity across all studies.

CBMA aims to identify clusters of foci that confirm convergency in activated regions between studies.[2] However, most approaches in CBMA are based on the limited assumption in spatial dependency among foci and cannot provide a straightforward and interpretable estimation of evidence of clusters in foci distribution.[3,4] Therefore, there is a need for models that postulates spatial dependency in foci distribution. Gibbs point processes (GPP) are a broad family of spatial processes that introduces a comprehensive definition of spatial dependency in a point pattern, called inter-point interaction.[5-7] Thus, GPP models allow us to quantify the evidence of cluster in pooled foci distribution using an interaction parameter and estimate the contribution of biological and other study-level features in foci distribution.

To demonstrate the benefits of the GPP models in the field of CBMA, we applied special kinds of them for the meta-analyze of the brain function alteration patterns in sleep deprivation (SD). SD is accompanied by cognitive and emotional impairments that affect attention and working memory, positive and negative emotion, and hippocampal learning.[8-11] Hence, it may precipitate the chance of medical errors, motor vehicle accidents, lower performance, and progression of neuropsychiatric or neurodegenerative disorders.[12–14] The relationship between SD, mental and physical disorders has affected brain function in various networks and it might expect studies on SD to report heterogeneous results from the brain activation pattern.[15] Moreover, the heterogeneity can be due to variation in biological or demographic features between studies or it can be influenced by unmeasured study-specific factors such as individual differences in participants.[4] Therefore, identifying brain regions affected by SD has become a complex problem. The main goal of this work is to utilize a meta-regression approach based on the GPP to quantify evidence of clusters in functional brain alterations patterns in acute SD while controlling for the effect of study features, especially SD duration.

Methods

SD dataset

Our investigations are motivated by the SD dataset from Javaheripour et al.[15] They sifted 29 eligible studies on acute SD. The average number of foci per study is 16.66 (range 1- 65) and the total number of foci is 483. The main study features were age, gender, sample size, imaging modality, and SD duration. Details are reported in Table 1. The main question concerning SD data is (i) is there evidence of cluster in foci distribution? (ii) is foci distribution affected by study features?

Table1. Descriptive statistics for SD data.

Characteristic	N = 291
Foci per study	16.66 (1-65)
Average of age per study	24.27 (20-32)
Percent of females per study	0.44 (0-1)
Sample size	21.31 (12-33)
Modality	
PET	3 (10%)
rsfMRI	2 (6.9%)
tfMRI	24 (83%)
SD duration	
Under 24	16 (55%)
Above 24	13 (45%)

Gibbs point process for CBMA

Suppose S eligible studies are selected for meta-analysis and the activity pattern related to i th study is denoted by a finite set of foci, $y_i=\{y_{ij} | y_{ij} \in B, j=1,...,n_i\}$, where B is the domain of the analysis and a is corresponds to a standard atlas of the brain, and n_i is the number of foci in a study. Using,[16] Gibbs probability density for pattern y_i can be written as

$$f(\boldsymbol{y};\beta_i,\gamma_i) = \alpha \left[\prod_{j=1}^{n_i} \beta_i(y_{ij})\right] \gamma_i^{C(\boldsymbol{y_i};R)},$$

where α is often an intractable normalizing constant. The parameter β(.)>0 is a first-order interaction function and governs the role of individual focus in the probability distribution. γ_i>0 introduces interaction parameter and C(y_i,R) is the interaction function. The idea of interaction functions is based on geometrical concepts. It depends on the points of y_i that lie within a distance R from each other and hence R called interaction range. By defining different interaction functions, different GPP can be created. The pairwise interaction functions are the simplest in which two points interact if they lie closer than the threshold distance R apart. However, for the point patterns acquired from neuroimaging studies that the probability of accruing a focus in a region is simultaneously related to reporting foci in the other brain regions, it is more realistic to use GPP with infinite-order interaction functions that probability density has contributions from all points in a pattern.

AI and GS models for SD data

Here, we focused on two widely used GPP, area-interaction (AI) and Geyer saturation (GS) point processes[5] that use infinite-order interaction functions. For the AI process, the interaction function is defined as follows

$$C(\boldsymbol{y_i},r) = n_i - \frac{\text{vol}\left(B \cap \left[\cup_{j=1}^{n_i} b(y_{ij},r)\right]\right)}{\pi r^2}, \quad (2)$$

where b(y_{ij}, r) is a disc with radius r centered at each y_{ij} and vol(.) denotes the volume. Hence, AI understands foci interaction as volume-based occupancy. The interaction function for the GS process is defined as

$$C(\boldsymbol{y_i},r) = \min\left(s, t(y_{ij},r,\boldsymbol{y_i})\right), \quad (3)$$

where s ≥ 0 is the saturation parameter and $t(y_{ij},r,y_i)$ is the number of another focus y_{ij}' lying within a distance r of the focus y_{ij}. We used a special case of s=1 where implies $t(y_{ij},r,y_i)$ is the nearest-neighbor distance for focus y_{ij}. It should be noted that the interaction range for both processes is $R=2r$.

A key feature concerning AI and GS models is that they quantify evidence of clusters in foci using interaction parameter γ_i. Values γ_i>1

describing a clustered while γ_i=1 describing a complete spatial randomness pattern (CSR) of foci. Hence, γ_i provides evidence that if a focus is reported, how much is likely than a CSR pattern to observe other foci in its neighborhood (i.e., interaction range).

We constructed a random effect meta-analysis model to estimate the effect of study features in the heterogeneity of foci distribution. Since the probability distributions are characterized by β_i (.) And γ_i parameters, a two-part model is suggested to create a line between study features and foci distribution as follow

$$\begin{cases} \beta_i(y_{ij}) = \exp(\theta^T X_i + \phi_i) \\ \gamma_i = \exp(\omega_0) \end{cases}, \quad (4)$$

where X_i=(X_1,..., X_p) denotes to p observable study features e.g., age, sample size, SD duration, etc. for study i and θ is the effect of the study features on β_i (y_{ij}). In addition, the effect of unobservable study-specific features is denoted by the latent random component ϕ_i, where $\phi_i \sim N(0, \sigma_\phi^2)$. Hence, the contribution of latent features is determined by σ_ϕ^2. We should note that equation[4] assumes γ_i be fixed across studies. We used spatstat library under R programming language to estimate interaction range and model parameters.[17]

Results

The first step of fitting AI and GS models to SD data was the estimation of interaction range. We should note that the primary purpose of the study was to test the evidence for clusters in the distribution of reported foci. Pairwise correlation function (PCF) is a useful tool that enables us to understand at which ranges we can observe clusters of the foci.[5] To have an integrated coordinates system for foci and ease the calculations for PCF, the foci were converted from the Talairach to MNI (Montreal neuroimaging institute) coordinate system using the Ginger ALE software and then normalized to a zero to one scale. Figure1 shows estimated PCF at different interaction ranges. It seems that foci lying within a distance less than 0.10 from each other tend to form a cluster. Hence, the radii of the interaction, *r*, is 0.05.

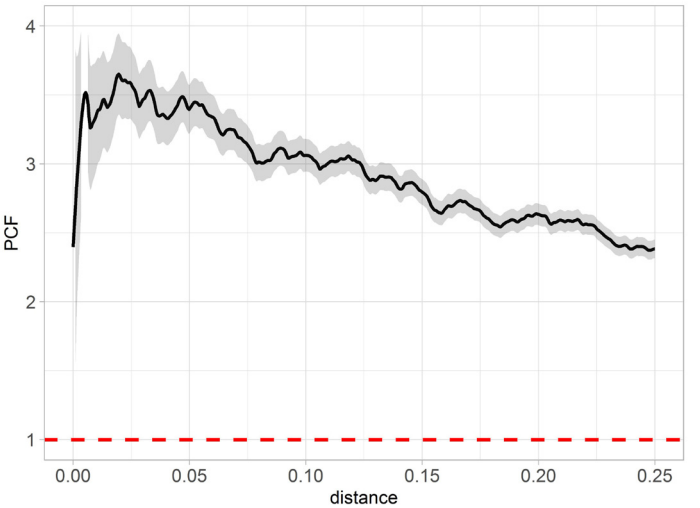

Figure 1. Determine interaction rage using pairwise correlation function (PCF): Estimated pooled PCF at different Euclidean distances (d) with 95% pointwise confidence bands. The dashed line is the pair correlation for the CSR process which is equal to 1 at all distances. PCF above or below this line provides evidence of clustering or repulsion, respectively.

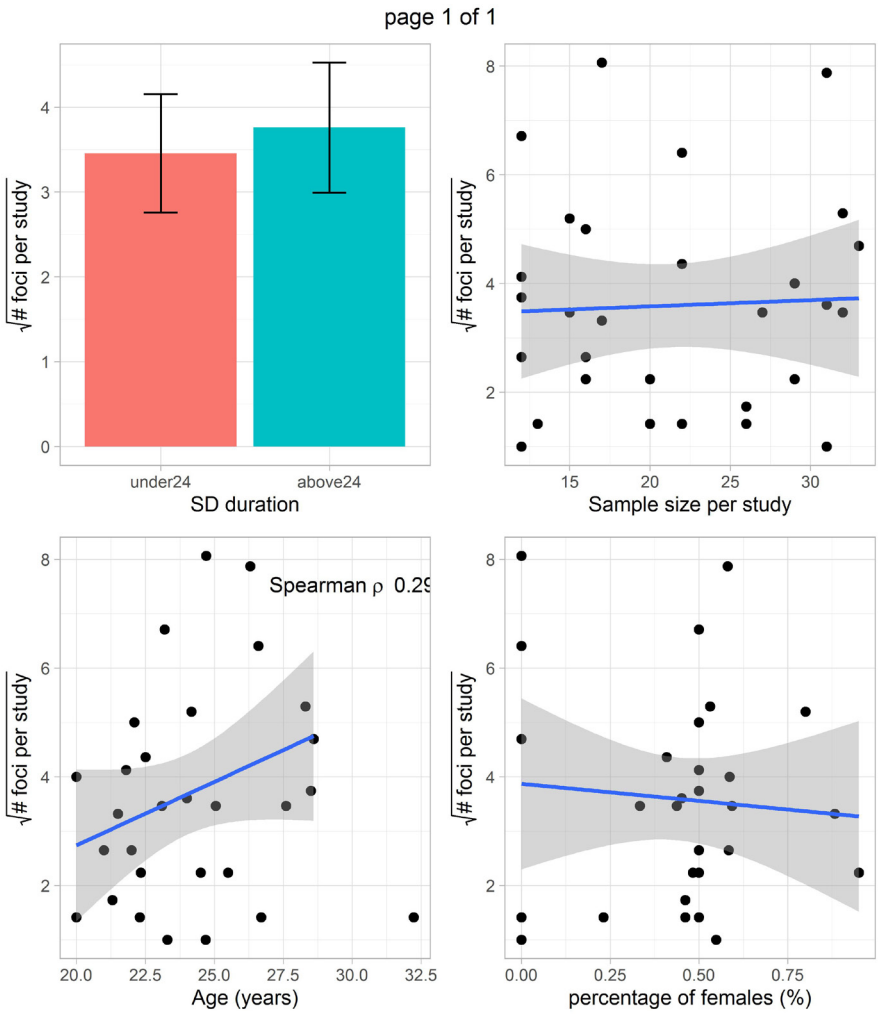

Figure 2.Explore the association between foci distribution and study features using foci counts (# foci). Blue lines are fitted using a simple regression model. For the age, we drop out one outlier and then fitted the regression model.

Table 2. Estimated parameters of the replicated Area-interaction and Geyer Saturationmodels for the SD dataset.

Sources of heterogeneity	Parameter	Area-interaction		Geyer Saturation	
		Estimate	p-value	Estimate	p-value
First-order interaction					
SD duration	θ_1	-0.11	0.41	-0.04	0.91
Age	θ_2	0.02	0.51	0.04	0.45
Latent factors	σ^2_ϕ	0.00071	-	0.51	-
Random noise	σ^2	1.73	-	1.74	-
Higher-order Interaction					
Intercept	ω_0	4.73	<0.001*	1.35	<0.001*
AIC		259542.4		248482.6	

*Significant at α=0.05.

The second step was to determine study features affecting foci distribution. We used exploratory techniques for feature selection. The square root of foci counts per study is a conventional outcome describing the spatial distribution of foci. Thus, the relationship between the foci counts and the study features was investigated. Figure 2 shows that except for the age covariate, other study features had a negligible association with square roots of foci counts. However, we included SD duration in equation[4] because our main hypothesis was that it has a significant contribution to the heterogeneity of foci distribution.

The results of fitting AI and GS models based on equation[4] are reported in table 2. The Akaike information criterion (AIC) denotes that the GS model has a better fit than AI. According to the GS model, the effect of SD duration on the β_i is negligible. However, the estimated variance of random effects σ_ϕ^2 is 0.51 which denotes $\frac{\sigma_\phi^2}{\sigma_\phi^2+\sigma^2} = 0.23\%$ of heterogeneity in $\log(\beta_i)$ is due to latent study-specific features. The estimated random effects ϕ_i is shown in a forest plot to better illustrate the heterogeneity across the studies (Figure 3). In addition, the estimated interaction parameter γi is 1.35 This provided strong evidence for a clustered distribution of foci due to SD (p-value <0.001). It means, for a reported focus, it's 35% more likely than a CSR pattern to observe other foci in its neighborhood.

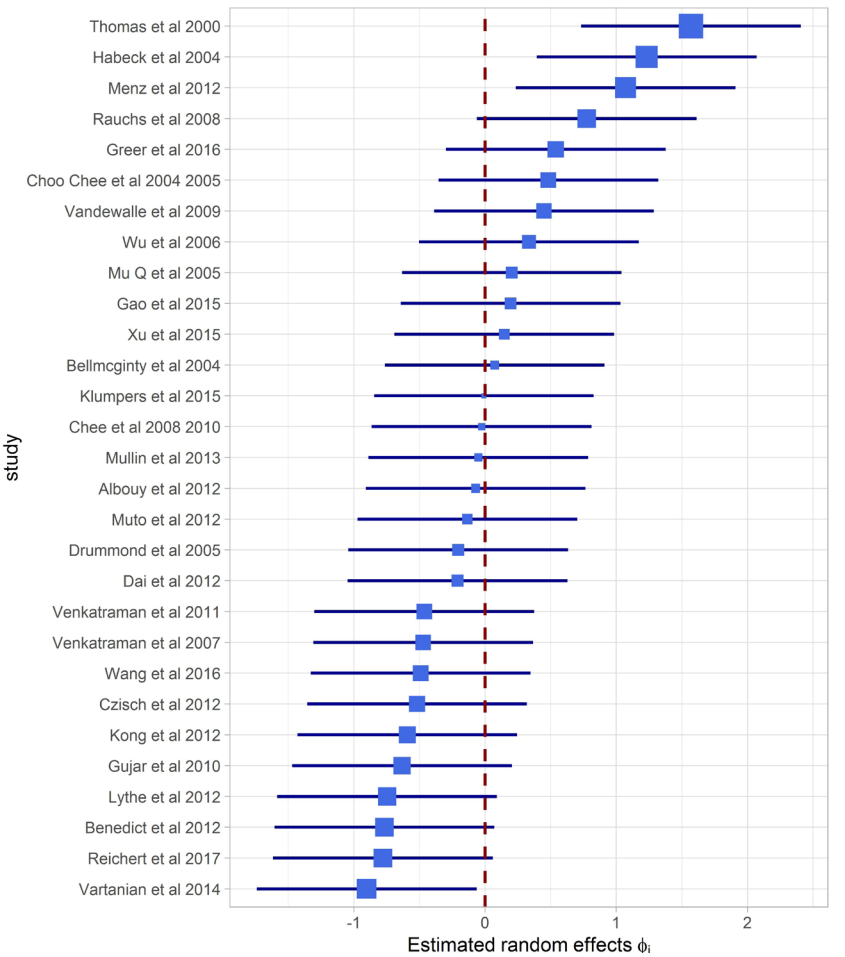

Figure 3. A forest plot that shows estimated based on equation (4).

Discussion

In this work, we utilized a meta-regression approach based on GPP models to combine foci acquired from functional brain alterations patterns due to SD. To the best of our knowledge, this is the first application of GPP in the meta-analysis of neuroimaging data. The key advantage of GPP based models is the introduction of the interaction parameter and interaction function which provide a comprehensive interpretation of the spatial dependency among foci. These models can quantify evidence of clusters in foci distribution using interaction parameter. In addition, GPP models can determine the contribution of study features to the observed heterogeneity in the foci distribution. Hence, We can use standard meta-analysis tools such as heterogeneity index (I^2) and random forest plot[18] for meta-analysis of coordinate data while conventional methods in CBMA such as ALE are not optimized for reporting these tools.[2]

We fitted two widely used GPP models, AI and GS, on the SD data. The AIC indicates that the GS model has a better fit. The results of the fitting GS model demonstrated that latent study-specific features have a fair contribution to the heterogeneity in foci distribution. This result confirms the variability in the spatial distribution of foci reported for each study. However, the effect of other study features such as age and SD duration was not statistically significant. Since most participants across all studies were in the same age condition, the result was expected for age. But for the SD duration covariate, the results contradicted our hypothesis. Numerous studies have shown that connectivity of different brain networks is affected by duration of SD for individuals with extended wakefulness.[19–21] Therefore, it was expected foci distribution for studies be affected by SD duration. The possible reason could be that studies with severe degrees of SD (e.g., above 49 hours) were not reported in the group with over 24 hours of SD. Therefore, the severity of SD for studies that reported above 24 hours of SD was not so high that brain function in them be significantly different from those with under 24 hours of SD. In addition, the estimated interaction parameter provided strong evidence for clusters in foci. In the previous work, Tahmasian et al. applied the activation likelihood estimation (ALE) method for the meta-analysis of the same data.[15] They confirmed the existence of clusters in the right intraparietal sulcus and superior parietal lobule.

Despite the new results obtained by the Gibbs models, the present study has a few limitations. Currently, the spatstat package is only able to fit Gibbs models in two-dimensional space . Thus, we had to project 3D images in 2D space and hence, the interaction parameter may be overestimated. Therefore, it is suggested to fit AI and GS models in 3D space for the future studies. Using a 3D Gibbs model, we can introduce a predictive index of activity such as conditional intensity to identify regions that correspond to clusters.

Conclusion

We attempted to introduce a new application of Gibbs models for the meta-regression of neuroimaging studies. Especially, we highlighted the role of the interaction parameter which provides evidence of clusters in pooled foci distribution. The application of GPP models for the meta-analysis of the SD

dataset enabled us to use well-established tools in common meta-analysis approaches such as forest plots and heterogeneity indices in CBMA. Overall, the results of the present study indicate that GPP models can be considereds a promising tool for neuroimaging meta-analysis.

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Conflict of interest disclosure

The authors declare no conflicts of interest.

Ethics approval statement

The study was approved by the ethics committee of Tarbiat Modares University (IR.MODARES.REC.1397.272).

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