Journal of Biostatistics and Epidemiology

J Biostat Epidemiol. 2023;9(3):363-377

Original Article

Task-Dependent Brain Activity in Generalized Anxiety Disorder Determined By Bayesian Spatio-Temporal Single Case Model

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ARTICLE INFO

Received 16.03.2023
Revised 21.03.2023
Accepted 26.04.2023
Published 15.09.2023

Key words:
Bayesian spatio-temporal model;
Functional magnetic resonance imaging;
Generalized anxiety disorder;
Emotional stimuli;
BOLD response;
Posterior probability map.

ABSTRACT

Introduction: Data obtained from functional magnetic resonance imaging (fMRI) have a complex structure. Considering the special features of this type of data in analyses is of particular importance. Previous studies on generalized anxiety disorder (GAD) as a prevalent mental disorder using functional neuroimaging have had conflicting results. In this study, we apply a Bayesian spatiotemporal model to this type of data which considers both spatial and temporal dependence among regions which is one of the most essential features to consider.

Methods: In this single-subject study, we analyze data from a patient with GAD and a healthy participant. Both participants are 24-year-old women who are assigned an emotion reactivity task (matching neutral and negative facial expressions) inside a scanner. The spatial Bayesian variable selection method is used to detect blood oxygen level-dependent activation in fMRI data.

Results: Activation areas in neutral and negative facial expressions are provided for both participants by posterior probability map. The results of our study show a greater level of activity in the GAD participant in comparison to the healthy participant in responding to the negative matching task.

Conclusion: the GAD patient showed more neural activity in response to negative facial expressions than the healthy participant in brain regions related to emotional response in the areas of the frontal Pole, middle frontal gyrus, insular cortex, and frontal orbital cortex. Moreover, the inferior frontal gyrus in the patient with GAD showed more reaction to negative emotional stimuli.

Introduction

Neuroimaging techniques have become a valuable tool for clinical research due to their ability to non-invasively study the structure and function of the brain with relatively high resolution. Functional magnetic resonance imaging (fMRI), as a technique of neural imaging, uses rapid MRI techniques which allow dynamic physiological processes to

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be performed on a scale of seconds. This feature can be used to spatially locate dynamic processes in the brain, such as neural activity.[1]

In an fMRI experiment, a participant is asked to do something in response to a series of stimuli, including cognitive, emotional, and other functions. The MRI machine then measures changes in blood oxygen levels in the brain at different time points.[2] In the vast majority of fMRI investigations, the BOLD (Blood oxygen level dependent) signal is measured. For our purposes, it is enough to know that the BOLD signal is an indirect measure of brain activity that is influenced by oxygenated and deoxygenated hemoglobin concentrations. When brain activity in a certain area increases, so does the metabolic demand, and the circulatory system responds by rushing oxygenated hemoglobin into that area. There is usually an oxygen need immediately after neural activity, and the influx of oxygenated hemoglobin into the area causes the BOLD signal to rapidly rise until it reaches a peak at roughly 6 seconds after the neuronal activity that provoked these reactions. The BOLD signal gradually returns to the baseline during 20 to 25 seconds after its peak.[3]

Generalized anxiety disorder (GAD) is a common and debilitating anxiety disorder that causes substantial distress, functional impairment, and financial costs.[4, 5] Excessive, pervasive, and uncontrollable worry is the hallmark of GAD. Irritability, restlessness, and impaired concentration are some of the symptoms associated with the disease. In addition, muscle tension, nausea, sweating, dry mouth, and diarrhea are somatic signs of GAD. This disorder is a recurring, chronic condition with a poor remission rate.[6]

In recent years and with the use of the fMRI technique, considerable efforts have been put into figuring out how the neurobiological underpinnings of this disorder work.[7]

For a better understanding of GAD, various cognitive models have been developed. Some studies have shown that people with GAD react to neutral facial expressions in the same way as they do to negative stimuli such as fear and anger facial expressions. For instance, in a study by Nitschke et al., it was found that patients with GAD had greater anticipatory activity than healthy participants in the bilateral dorsal amygdala preceding both aversive and neutral.[8] Even in a study by Holzel et al., it was found that compared to angry faces, GAD patients showed more neural reactions to neutral faces, with increased amygdala activity.[9] In other words, unlike many anxiety disorders, people with GAD find clues of threat and danger in neutral stimuli. However, this finding was not corroborated by other studies.[7] In a study by Montage et al., the results showed that patients with GAD were less sensitive to negative facial expressions than healthy participant.[10] In 2011, Palm et al. used the statistical method of analysis of variance to conclude that people with GAD are less sensitive to reacting to sad faces. The main finding in this study was less activity in the prefrontal among female participants while performing the emotional task.[11] In 2013, Bal et al. used a linear mixed-effects model that compared brain activity in GAD patients with healthy participants and observed lower brain activity in dorsolateral and dorsomedial PFC regions in the GAD group.[12] Another study showed that people with GAD were more active in responding to angry faces in the middle frontal gyruse, ACC, and PFC.[13]

In general, research on the neurobiological

features of GAD has yielded conflicting reports,[14] which hinder the generalizability of the results. In many fMRI experiments, the goal is to determine the activated areas of the brain and in order to achieve this goal, we must be able to infer four-dimensional data models. The present study is an fMRI single case-control study of a patient with GAD and a healthy participant in which we aim to identify activated areas of the brain in response to some emotional tasks using a Bayesian spatio-temporal model. Bayesian approaches[15] have a lot of potential in applications because they allow for flexible modeling of spatial and temporal correlations in data.[16] In reviewing the literature, as far as we know, no statistical method that considers both spatial and temporal correlations simultaneously has been used to identify the activated brain areas in GAD. Therefore, employing this method may lead to a deeper understanding of the disease.

Methods

Subjects

The data used in our single-subject study was extracted from a multi-subject research conducted in the National Brain Mapping Laboratory in Tehran (approval ID: IR.IUMS.REC.1397.274) on neural predictors of treatment response to cognitive behavioral therapy in patients with GAD. Sampling was done through an online advertisement for participant recruitment. The sample included 17 patients with GAD, who were selected using convenience sampling after conducting a diagnostic interview based on the Structured Clinical Interview for DSM-5 Disorders (SCID-5[17]) and considering the inclusion and exclusion criteria. Finally, one patient was excluded from the study due to lack of appropriate participation in the treatment process (failure to complete the therapeutic exercises and regular attendance at the treatment sessions) and one patient withdrew from the treatment session in the second session without mentioning the reason. Thus, the final sample for experiment group consisted of 15 patient with GAD. However, we will use only the data of one healthy individual and one patient in this research. The inclusion criteria were: (a) having a primary diagnosis of GAD based on SCID-5, (b) speaking fluently in Persian, and (c) being right-handed. The exclusion criteria were: (a) current episode of major depressive disorder, (b) symptoms of severe depression (BDI-II score 29 and above), (c) tendency to commit suicide, (d) current substance use/dependence disorder (in the past 6 months), (e) history of any psychotic disorder such as schizophrenia, bipolar mood disorder, (f) having a current or past major medical or neurological diagnosis such as heart surgery, or brain surgery and seizures, (g) taking psychiatric drugs (in the past 3 months) or participating in psychotherapy sessions (in the past 6 months), (h) pregnancy, (i) having inseparable metal objects in the body, and (j) claustrophobia. Due to the possibility of some confounding variables in the research such as the passage of time, the effect of participanting in the research or the effect of the experience of being inside the MRI scanner and, as a result, their effect on the finding of the experiment group, 15 individuals without physical and mental disorders were selected as yhe normal contral group after conducting a diagnostic interview based on SCID-5[17] and considering the inclusion and exclusion criteria. Participation in the study was voluntary and

informed written consent was obtained from the participants before the study began. The data used in our study were from a patient with GAD and a healthy participant, both 24-year-old women.

Tasks

In functional neuroimaging experiments, to evaluate the emotional reactivity in anxiety-related disorders in general and GAD in particular, facial expressions such as anger and fear are commonly used as triggers for stimulating the emotional areas of the brain.[7] The Hariri task,[18] which is an emotion-matching task, was employed to study the features of responding to emotional stimuli. This task consists of two conditions: negative facial expression matching and geometrical shapes matching.[18] The experiment design was block-wise. First, a 20-second rest block was presented, and then it was repeated between the task blocks. Each task block lasted for five seconds, and each task was repeated twice. It has been found that in patients with GAD, neutral stimuli can also stimulate the emotional areas of the brain.[9] As a result, in this study, a condition including neutral facial expressions was added to the two conditions of the Hariri task. Accordingly, participants performed three matching tasks of negative faces, neutral faces, and geometric shapes. According to Hariri's emotion-matching task, the first two conditions were subtracted from the third condition in order to find the activated emotional areas. A target stimulus is displayed on the top of the screen for the subjects inside the MRI scanner. Based on the instructions provided before scanning, they select one of the two response options at the bottom of the screen that corresponds to the target stimulus by pressing a key. They chose a face from the two faces shown at the bottom of the screen device that had an effect identical to the effect of the face shown at the top of the screen. Half of the images of negative faces belong to fear expression and the other half belong to anger expression. An equal number of men and women are selected in each series of faces. The stimuli were selected from the Nimstim set of facial expressions.[19]

Image Acquisition

MRI scans were acquired on 3.0 Tesla Siemens Magnetom Prisma at the Imaging Center of the Iranian National Brain Mapping Laboratory (NBML) (http://www.nbml.ir/). Images were acquired with 42 axial slices, 3-millimeter (mm) thick slices (T2*-weighted echo-planar imaging, voxel size = 3.0×3.4×3.4, TR = 2500 ms, TE = 30 ms, flip angle = 90°, Field of View = 218 mm, spacing = 0 mm, matrix size = 64×64 pixels, interleaved slice acquisition). There were 36126720 brain voxels in total.
Because the T1 images have a high spatial resolution, they are used for co-registration functional images. The parameters of the T1-weighted image are as follows: voxel size = 1×1×1 mm, TR = 2000 ms, TE = 3.47 ms, flip angle = 7°, Field of View = 256 mm, slice thickness = 1 mm, matrix size = 256×256 pixels.

Data Preparation and Preprocessing

Since the images in hand were raw, after changing the format from DICOM to NIFTI, it is necessary to pre-process to prepare the data for statistical analysis. Pre-processing was

performed using FSL, version 6.0.3, a piece of software under the Linux operating system for fMRI brain imaging data.[20] The following preprocessing steps were implemented: Brain Extraction (BET) for skull tripping with a threshold of 0.25, motion correction, slice timing correction, pre-whitening, registration to Montreal Neurological Institute space, and Full Width at Half Maximum (FWHM) was also considered equal to 5. The double-gamma function was used to convolve[21] the design matrix with the Hemodynamic Response Function (HRF). The process of head motion correction for both participants is shown in Figures 1-4, in which for rotational and translational motion in the direction of the x, y, and z axes, a process is drawn to determine the changes in each direction.

According to Figures 1, considering head motion correction parameters leads to a more accurate statistical model. Therefore, the design matrix in this study consists of 3 columns related to 3 matching tasks (geometric shapes, neutral faces, and negative faces), 6 columns related to motion correction parameters, and finally a column for intercept. All statistical

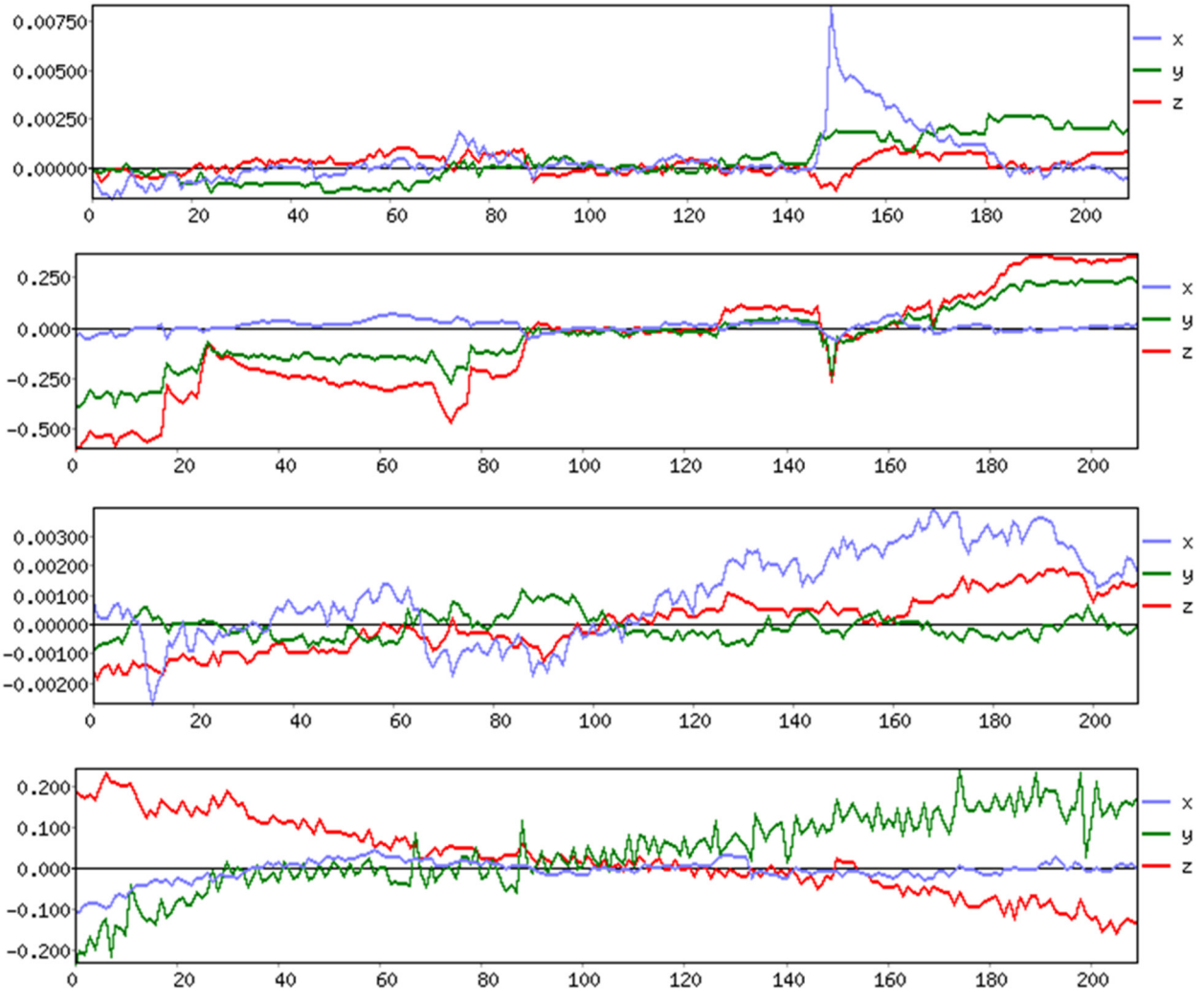


Figure1. Transitional correction of the healthy participant's head motion (mm)

analyses were carried out using R, version 4.1.1.

Statistical Analysis

One of the most important features of fMRI data is their temporal and spatial correlation. The temporal correlation originates from the fact that stimuli are offered continuously or regularly over time, and the reaction to a stimulus at time t is influenced by the stimulus at time t-1 as well as stimuli and reactions from earlier. In addition, since all of the voxels are contained in a single person's brain, spatial correlation also occurs. In three-dimensional space, in the vicinity of each voxel, there are 26 neighboring voxels. So, it is realistic to expect voxels that are adjacent to each other to have similar activation patterns.[22]

Due to the aforementioned features, the choice of a suitable statistical method that takes these features into account plays a significant role in the analysis of fMRI data. Most of the time, the massive volume of data and the complex structure of their spatial and temporal correlations become problematic. The high flexibility of Bayesian methods makes it possible to simultaneously consider both spatial and temporal correlations of fMRI data in modeling.[23]

In this study, a Bayesian spatio-temporal model was used to model BOLD signal variations for each voxel to make inferences about task-related changes in neural activity. The BOLD signal changes are spatially related among adjacent voxels, in addition to their intrinsic temporal dependency in a voxel.

When evaluating a change in BOLD contrast metabolism as a result of an external stimulus, the MR signal is hemodynamically delayed.[24] For statistical modeling of signal changes, it is necessary to model both spatial and temporal properties of voxels. Since the brain's hemodynamic response is a delayed version of the input time series, a mathematical operation is applied to the stimulus function to construct a delayed version that better fits the data. To take this time delay into account, the convolution operation can be used.[25]

For statistical analysis, a model is applied which has been discussed in detail by Musgrove et al.,[26] and briefly reviewed below.

The BOLD response over T time points is represented by a $T\times1$ vector voxel time series y_v (v=1,…,N) for v^{th} voxel and the model is

$$\mathrm{y}_v = \mathrm{X}\beta_v + \mathrm{R}_v\rho_v + \varepsilon_v\,, \quad \varepsilon_v \sim \mathcal{N}(0.\sigma_v^2\mathrm{I}), \quad (3.1)$$

which X is a $T\times p$ design matrix in which each column contains values from an impulse stimulation function and is convolved with HRF. To improve the accuracy of the model, we can consider the parameters of head motion correction in the design matrix. The vector β_v with a length of p, is the magnitude of the BOLD response to all stimuli, which captures the activation profile. The R_v denotes a $T\times r$ matrix of lagged prediction errors,[27] and ρ_v is a $r\times1$ autoregressive coefficient vector that is use d to model the temporal correlation. The error component in the equation is assumed to be independently normal distributed $N(0,\sigma^2 I)$.

The choice of the active voxel in this type of study is known as the variable selection problem, which is equivalent to determining non-zero coefficients fitted from a regression model.

The parameters are hierarchically assigned in the Bayesian framework and the corresponding priors are determined. A vector of binary random variables $\gamma_v=(\gamma_v1\ \ .....\gamma_{vp})'$ is added to

Table 1. The activated brain areas for the patient with GAD and the healthy participant (B=Bilatral, L=Left, R=Right).

	Negative matching task	MNI coordinates [X, Y, Z]	Neutral matching task	MNI coordinates [X, Y, Z]
GAD	B frontal pole B precentral gyrus L middle frontal gyrus R insular cortex R occipital pole L lateral occipital cortex, superior division R paracingulate gyrus L precuneous cortex L postcentral gyrus R fusiform gyrus R frontal orbital cortex R lateral occipital cortex, inferior division R inferior frontal gyrus, pars opercularis R fusiform gyrus	[0,60,2] [0,60,6] [46,6.1,27.03] [2,-24,64] [-41.14,18.81,30] [33.14,20.25,-6.7] [22,-92.7,-13.94] [-26.7,-66.36,45.11] [10.82,46.24,-2] [-4,-58,22] [-57.25,-8,27.03] [42,-64,-20] [42,18.15,-7.91] [44,-73.44,-5.5] [51.14,13.88,27.96] [42,-64,-20]	B precuneous cortex R superior frontal gyrus R frontal pole B postcentral gyrus L cingulate gyrus, posterior division R middle frontal gyrus L occipital pole	[0,-56,16] [6,-56,26] [6,14,52] [6,61.7,-3.9] [53.8,-16.67,30.62] [-52,-16,50] [0,-54,22] [38,34,32] [-24,-92,12]
Healthy	B central opercular cortex B postcentral gyrus B precentral gyrus R planum temporale L juxtapositional lobule cortex R lingual gyrus R fusiform gyrus R temporal pole	[60,-18,16] [-54,-18,10] [50,-18,56] [-44,-18,42] [4,-18,52] [-30,-18,62] [60,-18,8] [0,-6,56] [20,-76,-4] [22.75,-78,-3.96] [59.19,8.31,-3.96]	R cuneal cortex R supracalcarine cortex R intracalcarine cortex R lingual gyrus R occipital pole R fusiform gyrus R lateral occipital cortex, inferior division B lateral occipital cortex, superior division R insular cortex R frontal orbital cortex R supramarginal gyrus, posterior division L cingulate gyrus, anterior division	[3.92,-80.75,22.7] [4,-82,16] [4,-82,2] [4,-74.48,-0.82] [4,-92,0] [20,-74.48,-11.81] [38.43,-83.89,-7.1] [19.61,-60.36,57.22] [-22,-64,48] [44.16,10.18,-8] [44.16,16.51,-10.24] [44,-40,48] [-0.93,4.55,40]

indicate whether or not the voxel v is activated in response to a sequence of input stimuli. For regression coefficients, a spike-and-slab prior[28] was considered, which is defined as follows

$$\pi\left(\beta_{vj}|\gamma_{vj}\right)=\gamma_v\,\mathcal{N}\left(0.\tau_j^2\right)+\left(1-\gamma_{vj}\right)I_0\ .$$

Where, τ_j^2 denotes the stimulus-level variance, which is unknown and I_0 is a zero-mass point. For time-series correlation, the Autoregressive model of order 2[29] was employed in which coefficients have normal prior with zero mean and large variance. The value of 0.8722 was considered as the activation threshold of each voxel.[30]

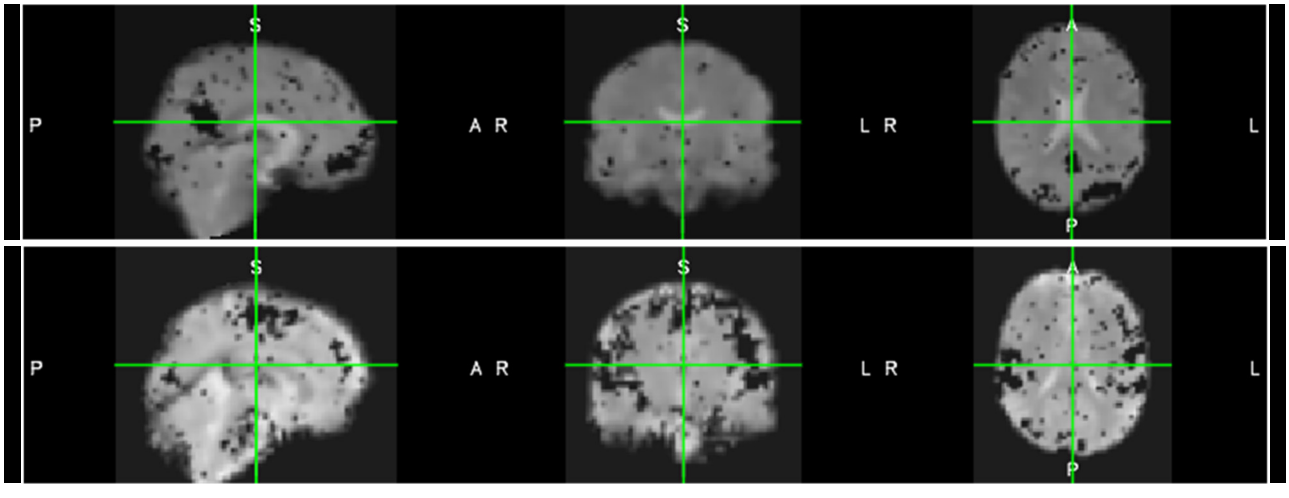
Results

After data preprocessing and fitting the statistical model (3.1), FSL was employed to identify the activated areas in the brain of the GAD and the healthy participants. Using Harvard-Oxford Atlas,[31] the activated areas in the brain of each participant during responding to our fMRI task were identified. The results are separately presented in Table 1 for the two negative and neutral conditions subtracted from the condition of the geometric shape. The coordinates of each activated area in the standard space were also reported.

Overall, in GAD patient, more regions, especially in the right hemisphere, were activated during the negative matching task, while few regions showed activation during the neutral matching task. The opposite was observed in healthy participants: the number of regions activated during responding to the neutral matching task, especially in the right hemisphere, was greater than that of the negative matching task. Additionally, in the GAD patient, compared to the healthy participant, more regions were activated during responding to the negative matching task, while in healthy participant, more regions were activated during the neutral matching task (Table 1). Another intreseting finding is that frontal regions (frontal pole, middle frontal gyrus, frontal orbital cortex, inferior gyrus, superior frontal gyrus) were primarily activated in GAD patient during responding to both tasks (Table 1).

The posterior probability maps of activation of the GAD and healthy participants are shown in Figure 2.

The black voxels have estimated posterior probabilities that exceed 0.8722, which show the activated points in the brain. This threshold



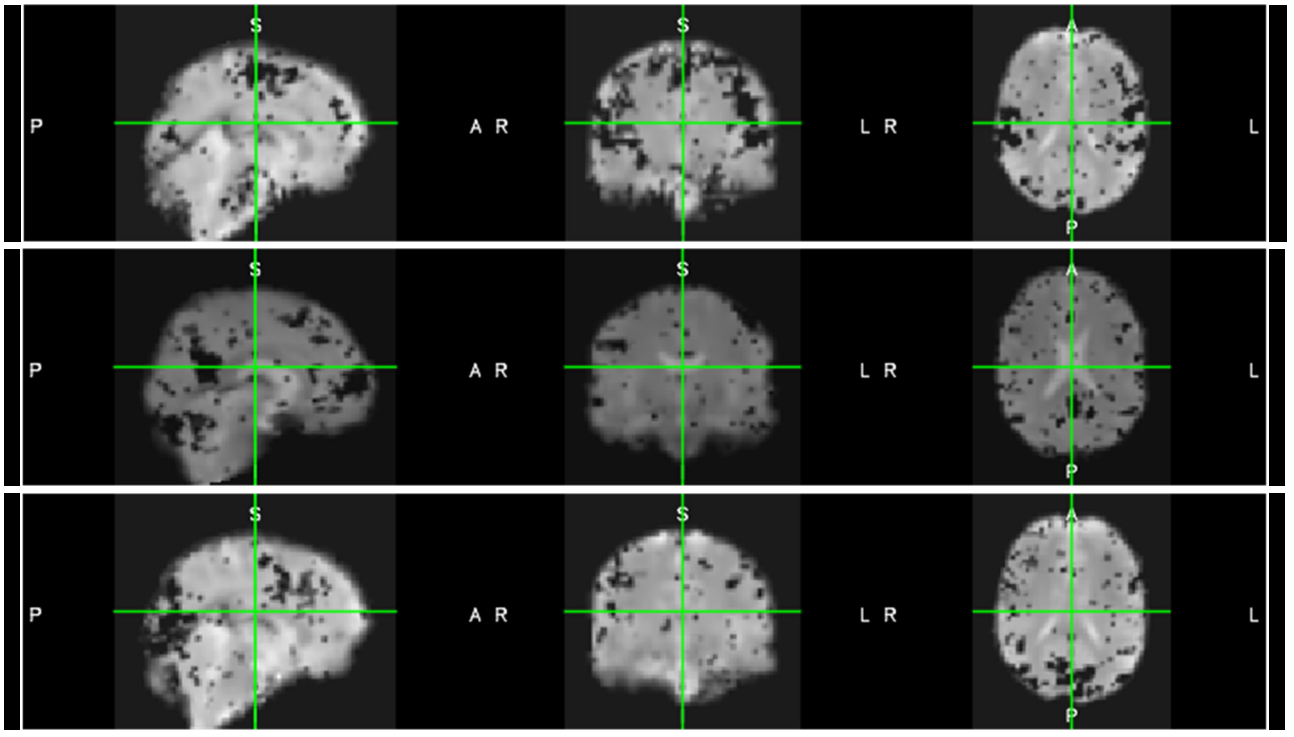


Figure 2. Healthy participant - neutral matching task

is equal to the p-value of 0.05.[30] In the negative matching condition, the GAD patient was more active as shown in Figures 5-8.

Discussion

This study aimed to use the Bayesian spatio-temporal model to identify activated regions of the brain in GAD in response to an fMRI task and compare it with a healthy individual. The specific features of fMRI data are of particular importance and need to be taken into account in analysis and modeling. Neglecting these features will cause an increase in errors in estimating and identifying activated areas of the brain. Sometimes considering the specific features of the data reduces the computational speed for which solutions must be provided. Bayesian spatio-temporal models are a statistical approach to fMRI analysis that account for both spatial and temporal dependencies among brain regions. This approach offer several advantages over traditional analytical methods, including: Improved accuracy and comprehensiveness, Bayesian spatio-temporal models can identify subtle changes in brain activity that may be missed by traditional methods. Additionally, can account for temporal dependencies between brain regions, which can help to better understand the underlying neural mechanisms of behavior. Increased robustness to noise, It can more effectively remove noise from fMRI data, which can improve the accuracy of results.[32] This model has been used in a variety of fMRI research applications, including identifying brain regions involved in emotion processing, examining changes in brain activity over time, and predicting behavior from brain activity.

In this research, by using parallel calculations, we compensated for the decrease in the

speed of calculations. The Bayesian spatio-temporal model has shown good accuracy and performance and is considered a flexible approach to analyzing fMRI data.[26]

The findings of research on GAD to date are somewhat controversial.[14] According to several studies, some areas of the brain in patients with GAD are more active in reaction to negative stimuli than healthy participants. However, some other areas have been reported less active compared with healthy participants.[10-12, 33]

An important finding of the present single-subject study is that the GAD patient showed more neural activity in response to negative facial expressions than the healthy participant in brain regions related to emotional response. More specifically, the areas of the frontal Pole, middle frontal gyrus, insular cortex, frontal orbital cortex, and inferior frontal gyrus in the patient with GAD showed more reaction to negative emotional stimuli compared to the healthy participant (in the case of the present study, angry or fearful facial expressions). This finding is in agreement with the findings of some previous studies.[34, 35]

In the literature, the participation of some prefrontal areas of the brain in the processing of emotional stimuli has been shown, especially in anxious people.[34, 35] In general, these results implied that the emotional reaction of the nervous system of patients with GAD in response to negative facial expressions was more than healthy people. Several previous studies have investigated the neural and psychological processes underlying emotional reactions and regulation in patients with GAD.[36-42] These researches are based on the assumption that these patients resort to worry due to underlying abnormalities in the regulation of emotional response, and they intend to control their intense emotional response in this way. There are two competing hypotheses to explain the neural basis of this emotional dysregulation. The first hypothesis, based on the conceptualization that there is a hyperactive top-down control system in GAD, suggests that patients with GAD show greater activity in the regulatory areas of the brain like the prefrontal cortex during the reaction to emotional stimuli and their regulation and this may decrease the activity of the emotional response areas of the brain, such as the amygdala, insula, and hippocampus. The second hypothesis suggests that patients with GAD have a weak response to regulatory areas in this context, and the activity of areas related to emotional response may increase, which indicates insufficient control of the top-down brain system.[14]

The findings of our study reflect the first hypothesis according to which increased activity of the prefrontal areas in GAD patients may underlie the most important symptom among these patients, namely worry.[14]

In other words, through their repetitive thoughts, these people try to make an estimate of possible risks in life and feel safe in this way although this method does not work successfully.[33, 43] The results of some other studies also accord with the first hypothesis. For example, Blair et al., have shown that in patients with GAD, an increase in the response to angry faces was observed in the frontal cortex, especially the medial frontal gyrus.[35] In another study by Monk et al., it was found that adolescents with GAD experienced more activity in the ventrolateral prefrontal cortex (the inferior frontal gyrus is located in this area) in reaction to angry faces as compared to healthy adolescents.[34] In a study using an

fMRI task, emotional response and regulation were evaluated in patients with GAD and it was found that the patients showed an increase in inferior frontal gyrus activity during the emotional response phase.[39] The findings of our study have important implications for our understanding of the neural basis of GAD. They suggest that emotional dysregulation, particularly in response to negative stimuli, may be a key underlying mechanism of this disorder.

It is important to bear in mind that these findings might not be generalized to all patients. As mentioned earlier, further research should be undertaken to investigate its generalizability.

Conclusion

In this research, a Bayesian spatiotemporal model was used which has been proposed for a single-subject analysis. There is abundant room for further progress in determining the activated brain areas in response to fMRI tasks in patients with GAD. Future fMRI single case studies on different patients with GAD should be undertaken to investigate the reproducibility of the results in which the results can be compared across studies. In future investigations, it might also be possible to adopt a different approach by performing a group analysis in which the results of single-subject analyses, conducted using the aforementioned method, are combined. This approach may facilitate developing a full picture of the disease and subsequently be of assistance to clinical practice In this research, a Bayesian spatiotemporal model was used which has been proposed for a single-subject analysis. There is abundant room for further progress in determining the activated brain areas in response to fMRI tasks in patients with

GAD. Future fMRI single case studies on different patients with GAD should be undertaken to investigate the reproducibility of the results in which the results can be compared across studies. In future investigations, it might also be possible to adopt a different approach by performing a group analysis in which the results of single-subject analyses, conducted using the aforementioned method, are combined. This approach may facilitate developing a full picture of the disease and subsequently be of assistance to clinical practi. In this research, a Bayesian spatio-temporal model was used which has been proposed for a single-subject analysis. There is abundant room for further progress in determining the activated brain areas in response to fMRI tasks in patients with GAD. Future fMRI single case studies on different patients with GAD should be undertaken to investigate the reproducibility of the results in which the results can be compared across studies. In future investigations, it might also be possible to adopt a different approach by performing a group analysis in which the results of single-subject analyses, conducted using the aforementioned method, are combined. This approach may facilitate developing a full picture of the disease and subsequently be of assistance to clinical practice. We hope that future research can build upon our findings and employ similar advanced analytical techniques to further elucidate the complex neurobiology underlying GAD and develop more effective treatment strategies for this prevalent mental disorder.

Data availability

Datasets generated and analyzed during the current study are available upon reasonable request.

Conflict of interest

The authors report there are no competing interests to declare.

Funding

No funding was received to assist with the preparation of this manuscript.

Authors' contributions

Hosseinian Qamsari and Rasekhi analyzed the data and drafted and revised the manuscript. Hosseinian Qamsari and Faghihzadeh helped in preprocessing the fMRI data and proofing the manuscript. Farrahi was responsible for preparing the data and interpreted the results. Farrahi was responsible for preparing the data, interpreting the results, and contributing to the design and execution of the research.All authors provided critical feedback, helped shape the research and manuscript, and approved its final version.

References

1. Woolrich MW, Jenkinson M, Brady JM, Smith SM. Fully Bayesian spatio-temporal modeling of fMRI data. IEEE transactions on medical imaging. 2004;23(2):213-31.

2. Lee K-J. Application of Spatial Bayesian Hierarchical Models to fMRI Data. Assessment of Cellular and Organ Function and Dysfunction using Direct and Derived MRI Methodologies. 2016:57.

3. Ashby FG. Statistical analysis of fMRI data: MIT press; 2019.

4. Wittchen HU. Generalized anxiety disorder: prevalence, burden, and cost to society. Depression and anxiety. 2002;16(4):162-71.

5. Hoffman DL, Dukes EM, Wittchen HU. Human and economic burden of generalized anxiety disorder. Depression and anxiety. 2008;25(1):72-90.

6. Kapczinski F, dos Santos Souza JJ, da Cunha AABM, Schmitt RR. Antidepressants for generalised anxiety disorder (GAD). Cochrane Database of Systematic Reviews. 2003(2).

7. Fonzo GA, Etkin A. Affective neuroimaging in generalized anxiety disorder: an integrated review. Dialogues in clinical neuroscience. 2017;19(2):169.

8. Nitschke JB, Sarinopoulos I, Oathes DJ, Johnstone T, Whalen PJ, Davidson RJ, et al. Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. American Journal of Psychiatry. 2009;166(3):302-10.

9. Hölzel BK, Hoge EA, Greve DN, Gard T, Creswell JD, Brown KW, et al. Neural mechanisms of symptom improvements in generalized anxiety disorder following mindfulness training. NeuroImage: Clinical. 2013;2:448-58.

10. Montagne B, Schutters S, Westenberg HG, van Honk J, Kessels RP, de Haan EH. Reduced sensitivity in the recognition of anger and disgust in social anxiety disorder. Cognitive Neuropsychiatry. 2006;11(4):389-401.

11. Palm M, Elliott R, McKie S, Deakin J, Anderson I. Attenuated responses to emotional expressions in women with generalized anxiety disorder. Psychological medicine. 2011;41(5):1009-18.

12. Ball TM, Ramsawh HJ, Campbell-Sills L, Paulus MP, Stein MB. Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorders. Psychological medicine. 2013;43(7):1475-86.

13. Maron E, Nutt D. Biological Markers of Generalized Anxiety Disorder. Focus. 2018;16(2):210-8.

14. Mochcovitch MD, da Rocha Freire RC, Garcia RF, Nardi AE. A systematic review of fMRI studies in generalized anxiety disorder: evaluating its neural and cognitive basis. Journal of affective disorders. 2014;167:336-42.

15. Cowles MK. Applied Bayesian statistics: with R and OpenBUGS examples: Springer Science & Business Media; 2013.

16. Zhang L, Guindani M, Vannucci M. Bayesian models for functional magnetic resonance imaging data analysis. Wiley Interdisciplinary Reviews: Computational Statistics. 2015;7(1):21-41.

17. First MB, Williams JB, Karg RS, Spitzer RL. User's guide for the SCID-5-CV Structured Clinical Interview for DSM-5® disorders: Clinical version: American Psychiatric Publishing, Inc.; 2016.

18. Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR. The amygdala response to emotional stimuli: a comparison of faces and scenes. Neuroimage. 2002;17(1):317-23.

19. Tottenham N, Tanaka JW, Leon AC, McCarry T, Nurse M, Hare TA, et al. The NimStim set of facial expressions: judgments from untrained research participants. Psychiatry research. 2009;168(3):242-9.

20. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004;23:S208-S19.

21. Hirschman II, Widder DV. The convolution transform: Courier Corporation; 2012.

22. Lazar NA. The statistical analysis of functional MRI data: Springer; 2008.

23. Lee K-J, Jones GL, Caffo BS, Bassett SS. Spatial Bayesian variable selection models on functional magnetic resonance imaging time-series data. Bayesian Analysis (Online). 2014;9(3):699.

24. Buxton RB, Frank LR. A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation.

Journal of cerebral blood flow & metabolism. 1997;17(1):64-72.

25. Henson R, Friston K. Convolution models for fMRI. Statistical parametric mapping: The analysis of functional brain images. 2007:178-92.

26. Musgrove DR, Hughes J, Eberly LE. Fast, fully Bayesian spatiotemporal inference for fMRI data. Biostatistics. 2016;17(2):291-303.

27. Penny W, Kiebel S, Friston K. Variational Bayesian inference for fMRI time series. NeuroImage. 2003;19(3):727-41.

28. Mitchell TJ, Beauchamp JJ. Bayesian variable selection in linear regression. Journal of the american statistical association. 1988;83(404):1023-32.

29. Montgomery DC, Jennings CL, Kulahci M. Introduction to time series analysis and forecasting: John Wiley & Sons; 2015.

30. Smith M, Fahrmeir L. Spatial Bayesian variable selection with application to functional magnetic resonance imaging. Journal of the American Statistical Association. 2007;102(478):417-31.

31. Makris N, Goldstein JM, Kennedy D, Hodge SM, Caviness VS, Faraone SV, et al. Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophrenia research. 2006;83(2-3):155-71.

32. Friston KJ, Harrison L, Penny W. Dynamic causal modelling. Neuroimage. 2003;19(4):1273-302.

33. Blair KS, Geraci M, Smith BW, Hollon N, DeVido J, Otero M, et al. Reduced dorsal anterior cingulate cortical activity during emotional regulation and top-down attentional control in generalized social phobia, generalized anxiety disorder, and comorbid generalized social phobia/generalized anxiety disorder. Biological psychiatry. 2012;72(6):476-82.

34. Monk CS, Nelson EE, McClure EB, Mogg K, Bradley BP, Leibenluft E, et al. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. American Journal of Psychiatry. 2006;163(6):1091-7.

35. Blair K, Shaywitz J, Smith BW, Rhodes R, Geraci M, Jones M, et al. Response to emotional expressions in generalized social phobia and generalized anxiety disorder: evidence for separate disorders. American Journal of Psychiatry. 2008;165(9):1193-202.

36. Borkovec TD, Alcaine O, Behar E. Avoidance theory of worry and generalized a nxiety disorder. Generalized anxiety disorder: Advances in research and practice. 2004;2004:77-108.

37. Mennin DS, Heimberg RG, Turk CL, Fresco DM. Preliminary evidence for an emotion dysregulation model of generalized anxiety disorder. Behaviour research and therapy. 2005;43(10):1281-310.

38. Goodwin H, Yiend J, Hirsch CR. Generalized Anxiety Disorder, worry and

attention to threat: A systematic review. Clinical Psychology Review. 2017;54:107-22.

39. Fitzgerald JM, Phan KL, Kennedy AE, Shankman SA, Langenecker SA, Klumpp H. Prefrontal and amygdala engagement during emotional reactivity and regulation in generalized anxiety disorder. Journal of affective disorders. 2017;218:398-406.

40. Fonzo GA, Ramsawh HJ, Flagan TM, Sullivan SG, Letamendi A, Simmons AN, et al. Common and disorder-specific neural responses to emotional faces in generalised anxiety, social anxiety and panic disorders. The British Journal of Psychiatry. 2015;206(3):206-15.

41. Etkin A, Schatzberg AF. Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. American Journal of Psychiatry. 2011;168(9):968-78.

42. Kim N, Kim MJ. Altered Task-Evoked Corticolimbic Responsivity in Generalized Anxiety Disorder. International Journal of Molecular Sciences. 2021;22(7):3630.

43. Behar E, DiMarco ID, Hekler EB, Mohlman J, Staples AM. Current theoretical models of generalized anxiety disorder (GAD): Conceptual review and treatment implications. Journal of anxiety disorders. 2009;23(8):1011-23.