Research Square

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Comparing VBM and ROI Analyses for Detection of Gray Matter Abnormalities in Patients with Bipolar Disorder using MRI

Seyedehsomayyeh Seyedi
Mashhad University of Medical Sciences
Raheleh Jafari
Mashhad University of Medical Sciences
Ali Talaei
Mashhas universtiy of Medical Sciences
Shahrokh Naseri
Mashhad University of Medical Sciences
Mahdi Momennezhad
Mashhad University of Medical Sciences
Maliheh Dadgar Moghaddam
Mashhad University of Medical Sciences
Hossein Akbari-Lalimi (H_Akbari_L@yahoo.com)
https://orcid.org/0000-0003-3753-8747

Research

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Abstract

Background: With the increasing efforts to a better understanding of psychiatric diseases, detection of brain morphological alterations are necessary. This study compared two methods-voxel based morphometry (VBM) and region of interest (ROI) analyses- to identify significant gray matter changes of patients with bipolar disorder type I (BP I). Methods: The structural MRI were obtained in a total of 50 subjects (25 healthy subjects with a mean age of 34.48±8.32 years as a control group and 25 patients with a mean age of 37.68±10.88 years). We compared the gray matter alteration results obtained by VBM analysis using the DARTEL approach with those obtained using ROI analysis which applies three probabilistic brain atlases namely, hammers, lpba40, and neuromorphometrics atlases. All analyses were conducted via the Computational Anatomy Toolbox (CAT12) implemented in Statistical Parametric Mapping (SPM12) software package. Results: The VBM findings suggested that gray matter reductions in left precentral and right precuneus of the patients compared to healthy subjects(α=0.0005, uncorrected). However, No regions reached the level of significance in ROI analysis using the three atlases (α=0.0005). Conclusion: It can be concluded that VBM analysis seems to be more sensitive to partial changes in this study. If ROI analysis is employed in studies to detect structural brain alterations between groups, it is highly recommended to use VBM analysis besides. Keywords: Voxel-Based Morphometry; ROI Analysis; bipolar disorder; MRI; brain.

1- Introduction

The brain is not a rigid organ and its structures change by different kinds of experiences and diseases. Localization of structural brain changes on magnetic resonance imaging (MRI) scans is a laborious issue in psychiatric diseases[1, 2]. Many investigators have been using MRI scans as a tool for diagnosis of neurological diseases or tracking disease progression, etc. Therefore, to help them, automated methods have been replaced to identify brain changes without the need for time-consuming manual measurement, and have grown in popularity since their introduction.

One of these automated methods is voxel-based morphometry (VBM) introduced by Ashburner and Friston[3]. This method is objective and able to perform a voxel-wise estimation to localize changes of a specific tissue. VBM commonly uses T1-weighted MRI scans and performs statistical tests across all voxels in the image to identify volume differences between groups. In VBM, there are three main preprocessing steps before statistical tests: segmentation, normalization, and smoothing.

The first step in preprocessing is segmentation. In this step, gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) and other tissues are extracted. Once an original brain image is used, it is primarily corrected for inhomogeneity of the magnetic field which affects the intensity values of the image voxel. This correction is called bias correction. Another factor that should be well addressed is the partial volume effect. The effect can occur at the boundaries of the tissues whose intensity values overlap[4]. By these corrections, the segmented tissue maps are produced.

To compare tissue segmented images, the images must be normalized. Normalization ascertains that different brain sizes, different head positions and somewhat different brain shapes of the subjects during MR imaging are corrected using linear and nonlinear normalizations although small differences still remain.

The final step of preprocessing is smoothing. In this step, the normalized segmented images are convolved with an isotropic Gaussian kernel. The output is a weighted average of each voxel's neighborhood. The underlying reasons for using smoothing are an increase of normality of residuals and signal to noise ratio and decrease of effect of misregistration between images[5].

After preprocessing, statistical analysis is performed on the images. It can be parametric using general linear model[3] or nonparametric[6, 7]. A statistical test demonstrates alterations in tissue volume between subject groups to a user-selected p-value. To remove false positives from the results, some methods such as family-wise error (FWR) correction or false discovery rate (FDR) correction could be applied[8, 9]. The final result is a statistical map localizing differences of a specified tissue between groups.

Three approaches of VBM include standard, optimized and DARTEL (Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm) [10–12]. The three approaches of VBM have been described in the literatures in detail[13, 14]. The difference between DARTEL and two first approaches is that using DARTEL, the high dimensional wrapping process was performed[13]. Therefore, misregistration and inaccuracies are reduced more between the template and individual images as well as credibility of the research is increased[15, 16].

The other method is an automated ROI analysis[17]. To perform this analysis, probabilistic brain atlases are employed. Probabilistic atlasing is a technique that generates anatomical templates and retains quantitative information on inter-subject variations across the population used to construct the atlas[18]. Using these atlases, it may solve problems of manual ROI assessment and increase repeatability of studies. Examples of these atlases are hammers, lpba40, and neuromorphometrics which are described below.

The three atlases are created using a label-based approach and based on multiple subjects. They are created using manual tracing on anatomical MRI from healthy subjects. The individual subject classifications are then registered to MNI space to generate a probabilistic atlas. The hammers, lpba40, and neuromorphometrics are composed of 69, 40 and 140 regions, respectively. These regions cover the whole cortex and the main subcortical structures. The probabilistic brain atlases have been detailed in the literatures [19–21].

More recently, the abovementioned automatic methods are being increasingly applied to detect the brain volumetric alterations[22] in psychiatric diseases such as Alzheimer's disease[23, 24], epilepsy[25], Parkinson's disease[26] and bipolar disorder[27, 28].

The present study had three objectives. The primary aim was to apply DARTEL VBM to detect structural GM changes in patients with BP I in comparison to the healthy group. The second aim was to compare the three probabilistic brain atlases i.e. hammers, lpba40, and neuromorphometrics atlases. The final aim of this study was to assess these methods i.e. VBM versus ROI analyses. It is hypothesized that a VBM analysis of the same data would complement the ROI findings. In the present study, we used Computational Anatomy Toolbox (CAT12) which is an extension to the SPM12 software package (Statistical Parametric Mapping).

2- Materials And Methods

2.1- Subjects

The subjects of the present study were 25 patients and 25 healthy people. Patients with BP I were selected by interview based on DSM-IV-TR criteria, direct assessment by two psychiatrists and medical records. Subjects were excluded if they had a history of substance misuse, neurological disease or closed head injury. The healthy group was included from a pool of community volunteers and assessed with the same criteria as the patient group as well as a lack of family psychiatric history. Table 1 summarized details of the demographic characteristics of the patient and healthy groups. Written informed consent was obtained from all participants and the study was approved by the local ethics committee.

Table 1.Demographic characteristics of participants.

Group	Age (years) (mean±SD)	Female/Male
HG†	34.48±8.32	19/6
PG††	37.68±10.88	18/7

† Healthy Group ††Patient Group

2.2- MRI Acquisition

High-resolution T1-weighted structural MR images were acquired at Qaem hospital, Mashhad, Iran, using a 1.5 Tesla symphony scanner (Siemens, Erlangen, Germany) with MP RAGE sequence (TR= 2300 msec, TE= 2.98 msec, flip angle =98°, field of view =256mmÍ256 mmÍ170mm, acquisition matrix =256Í 256, slice thickness= 1.27 mm) and the Digital Imaging and Communications in Medicine (DICOM) format.

2.3- Voxel Based Morphometry

For VBM analysis, the CAT12 toolbox implemented in SPM12 software was employed. The software run in MATLAB version 9.3 (The MathWorks, MA, USA). All 3D T1-weighted MR images were converted into the Neuroimaging Informatics Technology Initiative (NIFTI) format through SPM12. The images were

spatially normalized and segmented into GM, WM, and CSF tissue classes according to the DARTEL approach with default settings in 1.5mm cubic resolution and MNI space. The normalized maps were modulated with the resulting Jacobian determinant maps to preserve GM volumes of native space and smoothed with an 8 mm FWHM Gaussian kernel. The steps of segmentation, normalization, and modulation were automatically done in tandem in the CAT12 toolbox. Total intracranial volume (TIV), the native space volumes of GM, WM, and CSF maps were estimated as well.

In order to compare the results with ROI results, the GLM analysis was used with TIV as a covariate of no interest because, in ROI analysis, the effect of TIV was corrected. The two-tailed t-test was then generated using family-wise error (FWE) correction with a $p < 0.05$ and, additionally with an uncorrected $p < 0.0005$ thresholds. The extent threshold was set at 100 voxels. The processing framework of VBM analysis was shown in Fig.1.

2.4- ROI analysis

Using CAT12, regional tissue volumes were estimated in different regions based on the probabilistic atlases. All volumes are approximated in their native space using a high-dimensional spatial registration before any spatial normalization. By extracting data, GM volumes of different structures were determined. To remove the effect of variations in brain sizes, GM volumes of different structures were divided into TIV of the related subject and then the GM ratio of each region was obtained. Mann Whitney U test was used at the significance level of 0.05% (i.e. $\alpha=0.0005$, Bonferroni correction) for comparison of two groups using SPSS software, version 16 (IBM-SPSS, Armonk, NY, USA).

3- Results

3.1- The VBM analysis

In voxel by voxel analysis, no region showed significant alteration in healthy controls versus patients using FWE with p-value < 0.05 in the t-test. Nonetheless, when an uncorrected p-value <0.0005 was applied, two regions demonstrated lower GM ratios in the patients compared to the healthy subjects in the two-tailed t-test. It should be indicated that when the contrast, patients> healthy subjects, was selected, no brain regions exhibited significant alterations in the patients over the healthy controls. Fig. 2 and Table 2 detailed the related regions and MNI coordinates of the peak voxels.

Table 2.GM alterations detected by VBM.

P-value	Contrast	Location of the peak values	Cluster size (no. of voxels	MNI coordinates			t-value of the peak voxels
				X(mm)	Y(mm)	Z(mm)	
P<0.05 corr.	HG†>PG††	-	-	-	-	-	-
	HG<PG	-	-	-	-	-	-
P<0.0005 uncorr.	HG>PG	Left Precentral Gyrus	1204	-61.5	-10.5	43.5	5.115
		Right Precuneus	122	13.5	-63	22.5	3.949
	HG<PG	-	-	-	-	-	-

† Healthy Group ††Patient Group

3.2- ROI analyses

To compare the results of the ROI with those of VBM, the significant level of α<0.0005 was selected. None of the probabilistic brain atlases demonstrated a significant difference in GM ratios between the two groups

4- Discussion

4.1- Within VBM analysis

We performed a two-tailed t-test with a covariate of no interest (i.e. TIV) and compared the bipolar patients over the healthy controls in Table 2. Using p< 0.05 corrected, VBM analysis indicated no significant changes in GM volumes of the patients compared to those of the healthy subjects. The reverse contrast had the same result, as well. While the bipolar patients showed a significantly lower volume of GM in the left precentral gyrus and right precuneus than the healthy subjects, no region was higher in the patients than the controls using p<0.0005 uncorrected and extend threshold of 100.

To compare our VBM results with other studies' results, it should be noted that the results of VBM analyses of bipolar disorder are contradictory. Some studies reported no significant differences in gray matter volumes between patients and healthy subjects [29, 30] while other studies indicated alterations in different regions of the brain such as frontal gyrus[31, 32], temporal and parietal gyrus[33]. Besides, no study could replicate the same findings of previous studies. The reason for this may stem from using different procedures, thresholds, kernels, sample size, statistical corrections, as well as different inclusion criteria. Another reason can be that perhaps there are different subgroups in BP I, which have the same clinical manifestation but different mechanisms and origins. Overall, reported abnormalities of gray matter volumes are highly dispersed in bipolar disorder.

Taken all together, Our VBM results are somewhat similar to the fMRI study in which abnormalities in precuneus has been reported[34]. In the mentioned study, it was implicated that patients with bipolar disorder showed less activation posterior cingulate cortex/ precuneus compared to healthy controls. Also, Eker et.al mentioned a gray matter deficit in patients with bipolar disorder in comparison to unrelated healthy subjects in left precentral gyrus but right precuneus[35].

4.2- Within ROI analysis

ROI based analyses were conducted using the three probabilistic brain atlases. There were no regions reaching a significant level. However, the detected regions by VBM comes to appear when p- value increased to 0.02. Here, it should be noted that these atlases had several brain region labels such that some labels were similar but the other labels were different.

4.3- VBM vs. ROI

One of the aims of this research was to compare the results of VBM to the results of the ROI analysis on the same data set. For comparison, in VBM, a two-tailed t-test with TIV covariate of no interest was employed because replicating the main effects on ROI analysis was interested.

While VBM analysis found two regions of lower GM ratios- namely left precentral gyrus and right precuneus - in the patient group in comparison to the healthy group, the ROI analysis showed no difference in GM ratios between the two groups.

The reasons for these different results may stem from methodological differences between VBM and ROI methods, which can affect the results. Here, we have discussed it briefly.

In ROI analysis using a probabilistic atlas, an individual brain image was transformed and compared to the atlas as a template. This transformation may cause differences between the image and multiple images constructing the atlas. On the other hand, in a diseased population, local individual brain regions are highly variable and thus smaller regions or unusual conformation patterns are more subject to error when transforming. Therefore, appearing and vanishing of some differences may be caused due to inappropriate registration to the atlas.

In contrast to ROI analyses, VBM analysis conducted with CAT12 using the DARTEL approach enjoys precise registrations of images to the template to decrease misregistrations and inaccuracies. Although employing DARTEL does not yield a perfect registration, many differences due to misregistrations vanish and original anatomical alterations are coded. Furthermore, the selection of the level of significance and extend threshold are two factors that can have an effect on the results.

Another explanation for this difference is that in VBM, we search for differences in the images voxel by voxel rather than one region as a whole just like in ROI analysis. Consequently, if part of a region had a mild to moderate GM differences, this region might not reach a significant level in ROI analysis because the region might have the normal GM volume as a whole. Volume of precentral gyrus, for instance, is

6011 voxels in neuromorphometrics atlas but the volume of the alteration detected by VBM in this region is 1204 voxels. It means that the volume of the alteration is less than 25% of the overall volume. Therefore, such a small change may not be detected by the atlas. But as it could be seen in VBM, the analysis is able to detect partial abnormalities even in one region due to voxel by voxel search.

The two methods- VBM and ROI analyses- have advantages and limitations. VBM seem to succeed in the detection of partial differences in GM ratios. However, ROI analysis using the mentioned atlases may be more successful to detect moderate to severe GM abnormalities.

To our knowledge, this study is one of the first studies in patients with BP I using the CAT12 toolbox. But this study had some limitations. One of the limitation was the number of patients with BP I available during research. Another one was the lack of accessibility to the data set with predefined GM abnormalities. Hence, it is suggested that the similarity between the results of the two methods is investigated by the structural MR images with predefined GM changes with different degrees in severity.

5- Conclusion

We performed VBM and ROI analyses to detect brain changes in bipolar patients. DARTEL procedure and three probabilistic atlases are used. VBM could detect small changes. Therefore, it can be concluded that VBM analysis seems to be more sensitive to partial changes in this study. If ROI analysis is employed in studies to detect structural brain alterations between groups, it is highly recommended to use VBM analysis besides.

As mentioned, the results of the studies were dispersed for bipolar disorder. The result of this study emphasized it too. The divergence between the results highlighted the necessity of the design of more comprehensive research about bipolar disorder to take into account more psychiatric factors.

List Of Abbreviations

Full Name	Abbreviation
Voxel Based Morphometry	VBM
Region Of Interest	ROI
bipolar disorder type I	BPI
Computational Anatomy Toolbox	CAT12
Statistical Parametric Mapping	SPM12
Magnetic Resonance Imaging	MRI
Gray Matter	GM
white matter	WM
cerebrospinal fluid	CSF
Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm	DARTEL
Total intracranial volume	TIV
family-wise error	FWE
Healthy Group	HG
Patient Group	PG

Declarations

-Ethics approval and consent to participate:

Written informed consent was obtained from all participants and the study was approved by the local ethics committee.

-Consent for publication:

Not applicable.

-Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

-Competing interest:

The authors declare that they have no competing interests.

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-Author’s contribution:

AT and RJ contributed to assessing participants according to the mentioned criteria, taking MR imaging of them and giving consultation in terms of psychiatric issues. MD contributed as a statistical advisor. MM and SH. N contributed as advisors in terms of technical issues (image processing and analyzing). HA contributed as research assistance as well as a technical advisor. SS was a major contributor to image analyzing and writing the manuscript.

-Acknowledgements:

Not applicable.

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Figures

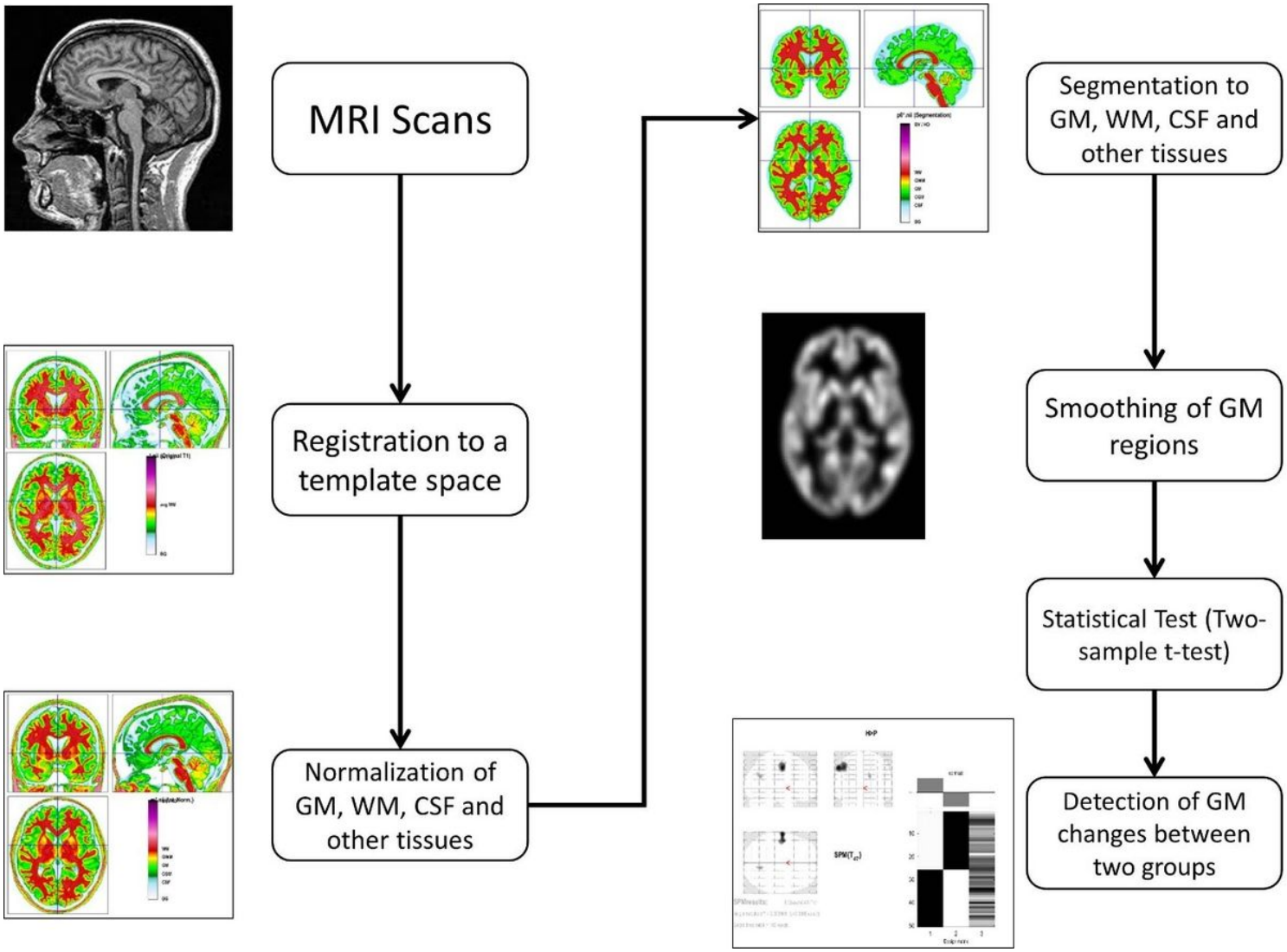
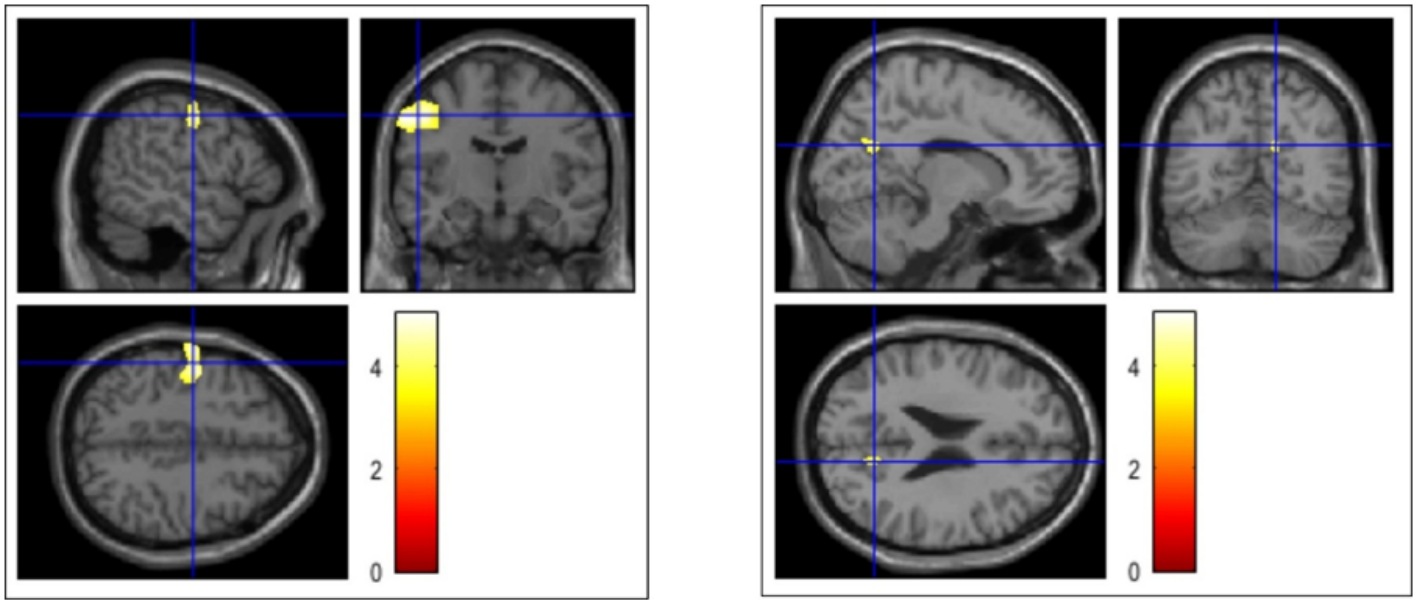


Figure 1

The processing framework of VBM analysis using the CAT12 toolbox of SPM software.



(a) (b)

Figure 2

The significant GM alterations revealed by VBM analyses with the covariate of no interest(TIV) in (a) Left Precentral Gyrus and (b) Right Precuneus when HG>PG. P-value <0.0005(Uncorrected) and extent threshold K=100.