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Comparing VBM and ROI analyses for detection of gray matter abnormalities in patients with bipolar disorder using MRI

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Abstract

Background: With the increasing efforts to a better understanding of psychiatric diseases, detection of brain morphological alterations is 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).

Results: The VBM findings suggested gray matter reductions in the left precentral gyrus 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, i.e., hammers, lpba40, and neuromorphometrics 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

Background

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

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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 (FWE) 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].

In this regard, Lagopoulos et al. found that there were potential changes in the WM content of the corpus callosum of BP I patients in the early stage of the disease using structural MRI and DTI and FSL software [29]. Several investigations indicated the WM and GM changes in different parts of BP patients' brains including the amygdala, hippocampus, and temporal and frontal lobes [30, 31]. Also, Mahon et al. proposed that deficits in dorsolateral prefrontal and limbic cortical structures were the main manifestations of BP disorder [32].

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).

Methods

Subjects

The subjects of the present study were 25 patients and 25 healthy people. It was conducted February 2017 to December 2018. 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. All patients were at their late remissions. They took lithium/valproate and antipsychotic medication. The most and the least numbers of the episodes were 17 and 1, respectively. The median number of episodes was 2.

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 summarizes 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[a]	34.48 ± 8.32	19/6
PG[b]	37.68 ± 10.88	18/7

[a]Healthy group
[b]Patient group

MRI acquisition

High-resolution T1-weighted structural MR images were acquired at Qaem Hospital, Mashhad, Iran, using a 1.5-T symphony scanner (Siemens, Erlangen, Germany) with MP RAGE sequence (TR = 2300 ms, TE = 2.98 ms, flip angle = 98°, field of view = 256mm × 256 mm × 170mm, acquisition matrix = 256 × 256, slice thickness = 1.27 mm) and the Digital Imaging and Communications in Medicine (DICOM) format.

Voxel-based morphometry

For VBM analysis, the CAT12 toolbox implemented in SPM12 software was employed. The software was 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 1.5 mm 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) and 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 uncorrected $p < 0.0005$ thresholds. The extent threshold was set at 100 voxels. The processing framework of VBM analysis is shown in Fig. 1.

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. The 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).

Results

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. Figure 2 and Table 2 detail the related regions and MNI coordinates of the peak voxels.

ROI analyses

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

Discussion

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 extent 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 [33, 34] while other studies indicated alterations in different regions of the brain such as frontal gyrus [35, 36], and temporal and parietal gyrus [37]. 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, and 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

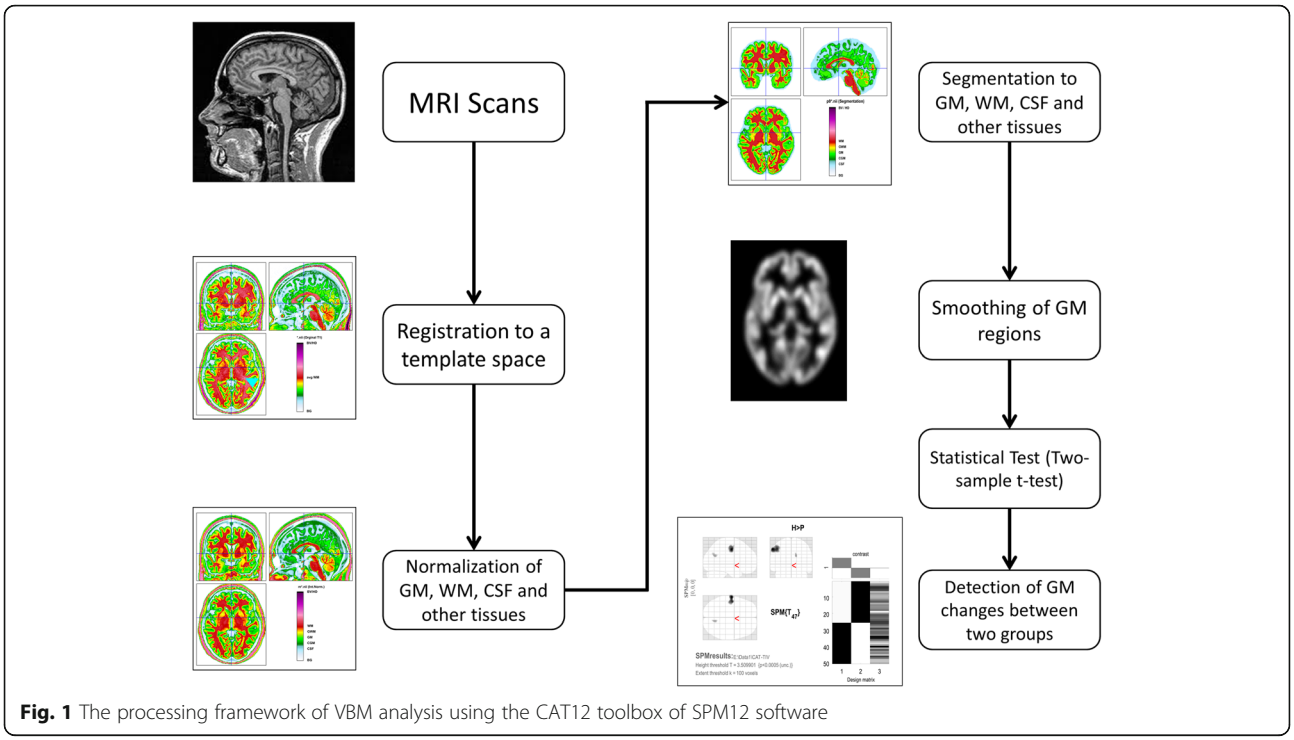

Fig. 1 The processing framework of VBM analysis using the CAT12 toolbox of SPM12 software

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 the precuneus has been reported [38]. In the mentioned study, it was implicated that patients with bipolar disorder showed less activation posterior cingulate cortex/precuneus compared to healthy controls. The precuneus is responsible for a wide range of cognitive functions including recollection and memory, integration of information related to the perception of the environment, cue reactivity, mental imagery strategies, episodic memory retrieval, and affective responses to pain [39]. The alteration in the functions of the precuneus may alter self-perception as well as the perception of the environment, resulting in behavioral changes that are evident in different episodes of BP.

Also, Eker et al. mentioned a gray matter deficit in patients with bipolar disorder in comparison to unrelated healthy subjects in the left precentral gyrus but right precuneus [40]. The precentral gyrus is the anatomical location of the primary motor cortex, responsible for the control of voluntary movement [41]. GM changes in the precentral gyrus may affect the primary motor cortex function and therefore cause less control on voluntary movement, as can be seen in BP patients.

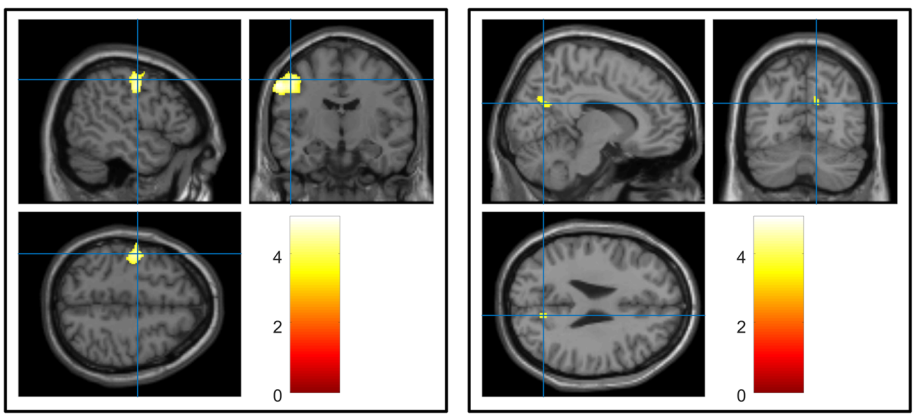

Fig. 2 The significant GM alterations revealed by VBM analyses with the covariate of no interest (TIV) in the **a** left precentral gyrus and **b** right precuneus when HG > PG. *p* value < 0.0005(uncorrected) and extent threshold *K* = 100

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[a] > PG[b]	–	–	–	–	–	–
	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	–	–	–	–	–	–

[a]Healthy group
[b]Patient group

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 come 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.

VBM versus 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 dataset. 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 the 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 image 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. The 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 seems 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 dataset 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.

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.

Abbreviations

VBM: Voxel-based morphometry; ROI: Region of interest; BP I: Bipolar disorder type I; CAT12: Computational Anatomy Toolbox; SPM12: Statistical Parametric Mapping; MRI: Magnetic resonance imaging; GM: Gray matter; WM: White matter; CSF: Cerebrospinal fluid; DARTEL: Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm; TIV: Total intracranial volume; FWE: Family-wise error; HG: Healthy group; PG: Patient group

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Authors' contributions

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 a research assistant as well as a technical advisor. SS was a major contributor to image analyzing and writing the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

Written informed consent was obtained from all participants, and the study was approved by the ethics committee of Mashhad University of Medical Sciences with Ref No. IR.MUMS.sm.1396.509.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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