Effects of Various Intracranial Volume Measurements on Hippocampal Volumetry and Modulated Voxel-based Morphometry

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Purpose : To investigate the effects of various intracranial volume (ICV) measurement methods on the sensitivity of hippocampal volumetry and modulated voxel-based morphometry (mVBM) in female patients with major depressive disorder (MDD).

Materials and Methods : T1 magnetic resonance imaging (MRI) data for 41 female subjects (21 MDD patients, 20 normal subjects) were analyzed. Hippocampal volumes were measured manually, and ICV was measured manually and automatically using the FreeSurfer package. Gray and white matter volumes were measured separately.

Results : Manual ICV normalization provided the greatest sensitivity in hippocampal volumetry and mVBM, followed by FreeSurfer ICV, GWMV, and GMV. Manual and FreeSurfer ICVs were similar in normal subjects ($p = 0.696$), but distinct in MDD patients ($p = 0.000002$). Manual ICV-corrected total gray matter volume ($p = 0.0015$) and Manual ICV-corrected bilateral hippocampal volumes (right, $p = 0.014$; left, $p = 0.004$) were decreased significantly in MDD patients, but the differences of hippocampal volumes corrected by FreeSurfer ICV, GWMV, or GMV were not significant between two groups ($p > 0.05$). Only manual ICV-corrected mVBM analysis was significant after correction for multiple comparisons.

Conclusion : The method of ICV measurement greatly affects the sensitivity of hippocampal volumetry and mVBM. Manual ICV normalization showed the ability to detect differences between women with and without MDD for both methods.

Index words : Hippocampus
Intracranial volume
Voxel-based morphometry
Volumetry
Magnetic resonance (MR)

Introduction

Intracranial volume (ICV) is used to estimate the volume of the premorbid brain in patients that undergo brain atrophy as a result of neuropsychiatric diseases (1). Because skull growth occurs along suture lines and is determined by brain expansion, which takes place

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during normal growth and development of the brain, ICV represents the size of the brain at maximal maturity unaffected by age and disease-related atrophy (2, 3). People with large intracranial volumes tend to have larger brain structures, so the volume correction of brain substructures, such as the hippocampus, is required in the field of volumetric analysis research.

The hippocampus is known to be involved in a number of conditions, including depression, schizophrenia, epilepsy, dementia, and sleep disorders, so magnetic resonance imaging (MRI)-based hippocampal volumetry has been widely used in studies of neuropsychiatric disorders (4). With the advances in image processing techniques in the late 1980s, precise methods for manual hippocampal volumetry were introduced, and validated with phantom studies (5–10). The detection of mild hippocampal atrophy and prediction of Alzheimer's disease, mild cognitive impairment, and mesial temporal lobe epilepsy became possible using thin-slice three-dimensional (3D) MRI with a slice thickness of 1-2 mm and advanced measurement techniques for brain volumetry (11–13).

Voxel-based morphometry (VBM) has been widely used for the analysis of gray matter or white matter density, and modulated voxel-based morphometry (mVBM) has also been used in analyses of the regional volume changes of gray matter or white matter in various neuropsychiatric disorders, such as schizophrenia, depression, epilepsy, and headache (14-18). In this process, spatially normalized images without modulation are used for analysis of brain tissue density, and modulated images are used for analysis of regional brain tissue volume changes. To preserve the total amount of signal during spatial normalization, areas expanded during warping are correspondingly reduced in intensity, while areas contracted during warping are increased in intensity. This process, known as modulation, involves multiplying tissue voxel values by the Jacobian determinants (i.e., the determinants of the deformation parameters obtained by spatial normalization). Therefore, the use of a modulation process may reflect regional volume changes. The unmodulated images preserve their own signal intensities, regardless of expansion or contraction during warping. Normalizing against the premorbid brain size is also an important factor for mVBM as the spatial normalization process matches the size and shape of the subject's brain to a template image at the time of the MRI scan, but does not normalize the premorbid brain size (19–22).

To find an accurate method for volume correction according to premorbid brain size, we evaluated the effects of ICV measurement on the sensitivity of hippocampal volumetry and mVBM. Hippocampal volume and mVBM were corrected by manually measured ICV or a verified automated method using FreeSurfer (FreeSurfer ICV). In addition, the control effects of the total volume of gray matter and white matter (GWMV), and gray matter volume (GMV) were also examined.

Methods

Subjects

Twenty-one female patients with major depressive disorder (MDD; range, 18–60 years of age) were recruited from among the patients of the Department of Psychiatry at our hospital. In addition, 20 healthy female control subjects, matched with regard to the age and handedness of MDD patients, were recruited from the community. This study was approved by the local institutional review board (IRB) of our hospital, and all subjects provided written informed consent prior to the study. After an initial psychiatric interview, all subjects underwent a physical examination and screening tests that included complete blood count, plasma electrolytes, liver function tests, thyroid function tests, and routine urine analysis.

Patients were included if they fulfilled the criteria for MDD based on the structured clinical interview (SCID) for DSM-IV (23). Depressive symptoms were assessed using the Beck Depression Inventory (BDI) (24) and the 17-item Hamilton Depression Rating Scale (HDRS) (25). Both SCID and HDRS were administered by an experienced psychiatrist. Patients were excluded from the study if they had a history of childhood trauma or other major Axis I disorders, including bipolar disorder, schizophrenia, schizoaffective disorder, claustrophobia, or a current or past history of alcohol or substance abuse or dependence. However, patients with underlying dysthymic disorders (i.e., double depression or panic attacks in the context of MDD) were included in the study. All patients were on antidepressant

medication, but none were taking antipsychotics or mood stabilizers. Control subjects had no personal or family history of Axis I disorders. No patient or control subject had been exposed to a traumatic event serious enough to cause post-traumatic stress disorder (PTSD). Subjects were also excluded if they had major medical or neurological illness, a history of significant head trauma, treatment with electroconvulsive therapy (ECT), exposure to oral or intravenous steroids, contraindications for MRI, or an IQ of less than 80.

MDD patients and the healthy subjects had mean ages (± standard deviation, SD) of 41.7 ± 11.00 (range: 21 ~ 57) and 41.9 ± 10.26 (range: 24 ~ 58) (years, respectively. All of the depressed patients and control subjects were right-handed, as assessed by the Edinburgh Handedness Inventory (26). The mean age of the first depressive episode was 33.2 ± 3.0 years, the mean number of lifetime depressive episodes was 3.9 ± 3.3, and mean illness duration was 80.0 ± 67.0 months. Five patients presented in their initial episode of depression, and 16 subjects had recurrent MDD. No patient showed atypical catatonic features or had postpartum onset. Psychotic symptoms, such as delusion and hallucination, were not reported by any patient. Four patients reported a family history of MDD.

MRI acquisition

All subjects were scanned with a 1.5-Tesla scanner (Gyroscan, Philips Medical Systems, Best, Netherlands). Coronal 3D T1-weighted turbo field echo (TFE) MRI was obtained with the following scanning variables: slice thickness = 1.3 mm, no gaps, 160 slices, scanning time of 10 min 13 s, repetition time/echo time (TR/TE) = 10/4.3 ms, number of signal averages (NSA) = 1, matrix = 256 × 256, field of view (FOV) = 22 × 22 cm, 160 slices, and 8° flip angle. Coronal slices were obtained perpendicular to the long axis of the anterior commissure (AC) to the posterior commissure (PC) in the midsagittal plane. The final voxel size was 0.86 × 0.86 × 1.30 mm (x × y × z). The Philips data format (.PAR/.REC) was converted to 16-bit Analyze format using the software MRIcro (http://www.sph.sc.edu/comd/rorden).

Manual ICV measurement

Preprocessing of T1 MRI data and manual volume measurements for ICV and the hippocampus were performed using a Unix-based Sun Ultra 1 Creator

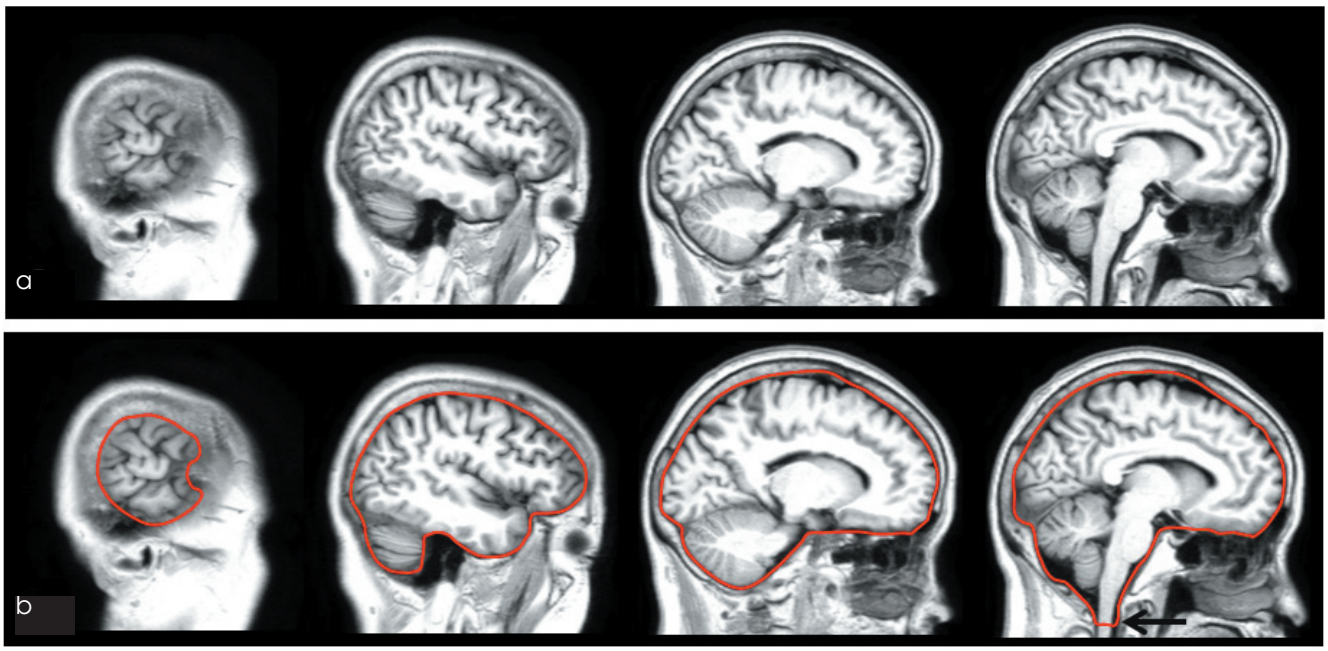

Fig. 1. The Boundary determination of ICV. Using 5-mm thickness sagittal MRI which was reconstructed from 1.3-mm thickness coronal MRI (a), the outer boundary of ICV was manually traced on the dura mater (b), and the lateral limits were defined as the most lateral slices of the brain parenchyma. The lower tip of the cerebellum was defined as the lower limit, and to establish the inferior boundary on the head tilt-corrected sagittal images, a horizontal line was drawn across the midbrain to include the lower tip of the cerebellum (black arrow).

workstation (Sun Microsystems, Santa Clara, CA), and Analyze 7.5™ (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). ICV was used to normalize hippocampal volumes, and to correct for variations in individual brain size for mVBM (3).

To measure the ICV, the original T1-weighted TFE MRI data were reconstructed to create 5-mm thick sagittal images, which were then magnified twofold. The cerebrum, cerebellum, and midbrain were included in the ICV volume with the outer boundary of dura mater (27–30). The lateral limits of the ICV were defined as the right- and left-most slices of the brain parenchyma on sagittal images, and the lower tip of the cerebellum was defined as the lower limit. We increased the brightness of the image to improve the visual clarity of the boundary of the dura mater. Using the established measurement criteria (30), the dura mater of the cerebrum, the cerebellum, and the midbrain (except for the inferior boundary) were traced manually (Fig. 1). To establish the inferior boundary on the head tilt-corrected sagittal images, a horizontal line was drawn across the midbrain to include the lower tip of the cerebellum (28). The details of the ICV measurement were illustrated in our previous paper (31).

FreeSurfer automated ICV measurement

The automated measurement ICV was processed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu). Coronal MRI results were reformatted to axial images without interpolation, and then the Analyze format was converted to the FreeSurfer mgz format. The process of FreeSurfer's ICV estimation was previously described in detail in a developers' publication (32). Briefly, the template image embedded in FreeSurfer was constructed from 24 adults. The MRIs of all subjects were registered to the template image using a 12-parameter affine transformation, and the registration of individual images to the template image generated the Atlas Scaling Factor (ASF). The ASF value larger than 1 represents the expanded volume or less than 1 represents contracted volume (32).

Hippocampal volumetry

The methodological details of hippocampal volumetry were precisely described in our previous paper (33). From the anterior head to the posterior tail, including the cornu ammonis, gyrus dentatus, hippocampus, and subiculum, the entire hippocampal volume was measured. The anterior boundary of the hippocampus was identified as the alveus. The lateral border of the hippocampus was delineated against the entorhinal cortex by the upper margin of the white matter of the subiculum. The posterior end of the hippocampus was taken as the point at which the tail of the hippocampus disappeared. The rater manually traced the alveus according to the defined hippocampal boundary criteria.

Voxel-based morphometry

To investigate the gray matter volume change, mVBM was performed using SPM2 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK) implemented in MATLAB 7.0 (MathWorks, Natick MA) and Gaser's VBM toolbox (http://dbm.neuro.uni-jena.de/vbm) (20, 21). To create customized templates and prior images of the gray matter, white matter, and cerebrospinal fluid (CSF) distributions, MRI data from normal subjects and MDD patients were spatially normalized to the standard Montreal Neurological Institute (MNI) T1 template. Normalized images were segmented into gray matter, white matter, and CSF, and sub-sampled into a voxel size of $2 \times 2 \times 2$ mm. To remove isolated voxels of one tissue class unlikely to be members of this tissue type, the hidden Markov random field (HMRF) model was applied in all segmentation processes (34). The spatially normalized raw images and segmented gray matter, white matter, and CSF images were averaged and saved into the customized T1 template as gray matter, white matter, or CSF prior images, respectively. Finally, three prior images, and customized T1 template were smoothed using an 8-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel (IGK).

The raw T1 images of all subjects were automatically segmented into gray matter, white matter, and CSF partitions in native space, and the volumes of gray and white matter images were then calculated. Spatial normalization parameters were estimated by matching individual gray matter with the corresponding gray matter template of the present study, and then spatially normalized images of the original images were created. Spatially normalized images were segmented using the

HMRF operation and corresponding prior images (gray matter, white matter, and CSF partitions). The spatially normalized gray or white matter images were modulated by the Jacobian determinants derived from spatial normalization for regional volume change analysis, and finally modulated images were smoothed using an 8-mm FWHM IGK. The final voxel size for VBM analysis was 1 × 1 × 1 mm.

Coordinates were defined by the MNI coordinate system, and cluster regions were named as described in the atlas of Duvernoy (35). The images were displayed in neurological views (right hemisphere of the brain is shown on the right of the images).

Statistics

Statistical analysis was performed with SPSS 11.5 (SPSS Inc., Chicago, IL). Volume differences in ICV, gray/white matter, and both hippocampi between normal subjects and MDD patients were examined using the t-test. To correct for the effects of age or age and ICV, analysis of covariance (ANCOVA) was also performed. The intraclass correlation coefficients (ICCs) for intra-observed reliability were tested using 10 subjects (five normal subjects, five MDD patients) using Cronbach alpha model (36). All tests were two-tailed, and the level of significance was $p < 0.05$.

For mVBM analyses, ANCOVA using (1) age and manual ICV, (2) age and FreeSurfer ICV, (3) age and total volume of gray and white matter, or (4) age and gray matter volume as covariates were performed separately for regional volume change analyses using modulated gray matter images. To provide a consistent statistical level, the four mVBM results were compared at the level of uncorrected $p < 0.001$, and clusters were excluded when the cluster size was less than 200 voxels (k_E > 200 voxels, 200 mm3). To correct for multiple comparisons, the results of each mVBM which analyzed with four confounders (manual ICV, FreeSurfer ICV, GWMV, and GMV) were corrected using a false discovery rate (FDR) and family-wise error (FWE) corrections at the level of $p < 0.05$, and the extent threshold was set to k_E > 200 voxels.

Results

The age distributions among healthy female subjects and female MDD patients were similar ($p = 0.956$). The ICCs for hippocampal volumetry were 0.947 and 0.934 for the right and left hippocampus, respectively, and the ICCs for manual ICV, FreeSurfer ICV, GWMV, and GMV were 0.996, 1.000, 1.000, and 1.000, respectively.

ICV

The mean ICV between normal subjects and MDD patients was very similar upon manual ICV measurement ($p = 0.94$, two-tailed t-test), and did not differ upon FreeSurfer ICV measurement ($p = 0.23$, two-tailed t-test; Table 1). ICVs determined using the manual versus FreeSurfer methods did not differ among normal subjects ($p = 0.70$, two-tailed paired t-test), but the FreeSurfer ICV was significantly smaller than the manual ICV in MDD patients ($p = 0.000002$,

Table 1. The Effects of Various ICV Controls in Hippocampus and Gray/White Matters

	Normal Controls (SD)	MDD Patients (SD)	AI (%)	P	ICV_{MAN} P*	ICV_{FS} P**	GWMV	GMV
Intracranial volume								
Manual	1396.97 (123.52)	1393.55 (170.84)	0.25	0.94	—	—	—	—
FreeSurfer	1385.40 (108.20)	1328.46 (182.29)	4.20	0.23	—	—	—	—
P$^{\$}$(manual : FreeSurfer)	0.70	< 0.0001						
Gray matter	665.25 (48.97)	622.95 (82.45)	6.57	0.054	0.0002	0.06	—	—
white matter	388.16 (34.33)	374.51 (51.79)	3.58	0.33	0.13	0.72	—	—
Manual								
Right Hippocampus	2.87 (0.28)	2.66 (0.41)	7.59	0.061	0.014	0.13	0.33	0.45
Left Hippocampus	2.81 (0.23)	2.56 (0.38)	9.31	0.03	0.004	0.07	0.18	0.30

MDD, major depressive disorder; SD: standard deviation, volumes were represented in cm3; ICV, intracranial volume;
"ICVMAN, manual ICV; ICVFS, FreeSurfer ICV; GWMV, the total volume of gray and white matters; GMV, gray matter volume;
AI, Asymmetric volume Index (Normal - MDD) / {(Normal + MDD)/2} × 100 %; P, ANCOVA using age as a covariate, t-test; P$^{\$}$, paired t-test, ANCOVA using age and ICV (measured manually* or by FreeSurfer**) as covariates.

two-tailed paired t-test; Table 1, Fig. 2).

Gray and white matter volumes

The absolute GMV showed marginal significance (p = 0.054, t-test) between normal and MDD subjects. However, the manual ICV-corrected GMV of MDD patients was significantly smaller than that of normal subjects (p = 0.00015, ANCOVA using manual ICV and age as covariates). However, the FreeSurfer ICV-corrected GMV differed at the marginal significance (p = 0.059, ANCOVA using FreeSurfer ICV and age as covariates). White matter volume did not differ significantly between groups in terms of absolute volume or volume corrected by manual or FreeSurfer ICV (Table 1).

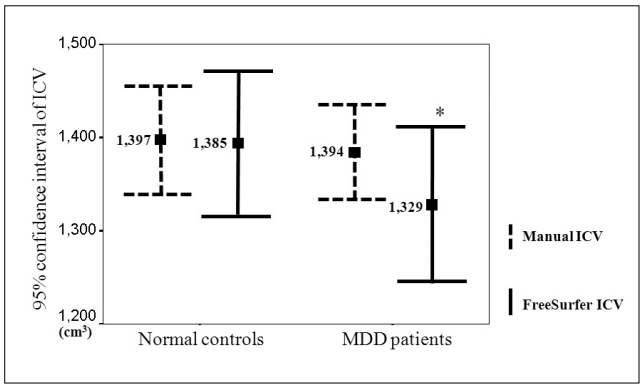

Fig. 2. Error bars for comparison between manual and FreeSurfer ICV measurements. In normal subjects, the mean ICV did not differ between manual and FreeSurfer methods. However, the mean ICV was significantly different between manual and FreeSurfer methods in MDD patients (See Table 1). The square plots of the error bars represent the mean ICV and upper and lower limits of the 95% confidence interval.

Hippocampal volume

The absolute left hippocampal volume of MDD patients was significantly smaller than that of normal subjects (p = 0.029), but no significant difference in right hippocampal volume was observed between groups (p = 0.061; Table 1). The left and right hippocampal volumes of MDD patients corrected by manual ICV were significantly smaller than those of normal subjects (right, p = 0.014; left, p = 0.004; ANCOVA using manual ICV and age as covariates), but none of the remaining volume correction methods (i.e., FreeSurfer ICV, GWMV, or GMV) showed significant

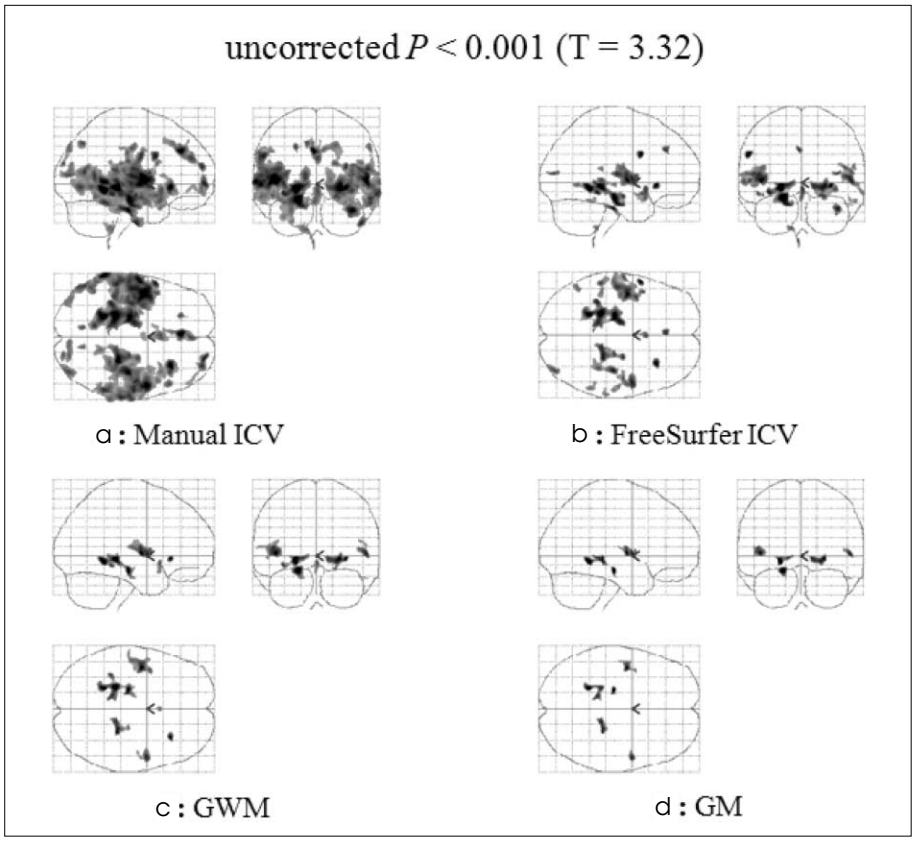

Fig. 3. Results of modulated voxel-based morphometry (mVBM) controlled by various ICV measurements. The decrease in gray matter volume was most significant in the results of mVBM corrected by manually calculated ICV (a2). In contrast, the mVBM results corrected by FreeSurfer ICV (b), gray and white matter (GWM) (c), and gray matter (GM) alone (d) were less sensitive in detecting GMV changes. In all analyses, the level of statistical significance was set to uncorrected p < 0.001 (T = 3.32), and noisy clusters with voxel counts less than 200 voxels were excluded.

differences in volume between normal subjects and MDD patients.

Modulated voxel-based morphometry

The mVBM results corrected by manual ICV showed reduced GMVC in the bilateral inferior frontal gyri, right anterior insular cortex, bilateral posterior insular cortices, superior frontal gyri, gyri rectus, hypothalami, whole hippocampi, anterior and posterior parahippocampal gyri, superior and inferior temporal

Table 2. Comparisons of mVBM Results Corrected by Various Confounders

Location	Side	MNI Coordinates (mm)			T	FDR P*	Puncorr
		x	y	z			
Manual ICV-corrected							
inferior frontal gyrus	R	57	−17	38	4.59	0.003	< 0.00002
inferior frontal gyrus	L	−60	−7	31	5.06	0.002	< 0.000006
insula	R	38	24	−7	4.89	0.002	< 0.000006
insula	L	−44	−5	3	6.35	0.001	< 0.000001
superior frontal gyri	B	0	46	28	4.95	0.002	< 0.00008
gyri rectus	B	−2	13	−19	4.62	0.003	< 0.00002
hypothalamus	B	0	−4	−8	3.56	0.009	< 0.0005
hippocampus	R	24	−11	−14	4.66	0.003	< 0.00002
hippocampus	L	−23	−13	−17	4.70	0.003	< 0.00002
parahippocampal gyrus	R	15	−51	5	4.17	0.009	< 0.0005
parahippocampal gyrus	L	−21	−51	−4	5.68	0.001	< 0.000001
superior/middle temporal gyrus	R	60	−20	−3	4.61	0.003	< 0.00002
superior/middle temporal gyrus	L	−61	−20	8	4.99	0.002	< 0.000008
fusiform gyrus	R	39	−20	−29	5.78	0.001	< 0.0000006
fusiform gyrus	L	−22	−47	−7	6.72	0.001	< 0.00000003
FreeSurfer ICV-corrected							
superior frontal gyrus	L	−3	36	35	4.35	0.056	0.00005
insula	R	31	25	−4	4.80	0.056	0.000012
insula	L	−47	−5	4	4.39	0.056	0.000047
gyri rectus	B	0	13	−19	3.80	0.056	0.00025
hippocampus	R	24	−10	−15	4.27	0.056	0.000012
hippocampus	L	−19	−20	−15	5.23	0.056	0.000003
superior temporal gyrus	R	53	0	2	4.41	0.056	0.000041
superior temporal gyrus	L	−62	−9	2	4.06	0.056	0.00013
middle temporal gyrus	R	60	−19	−2	3.78	0.056	0.00027
fusiform gyrus	R	39	−20	−29	4.50	0.056	0.00003
fusiform gyrus	L	−22	−47	−7	5.11	0.056	0.000005
Gray and white matter volume (GWMV)-corrected							
insula	R	31	25	−4	4.52	0.16	0.000029
insula	L	-47	−5	4	4.22	0.16	0.00006
gyri rectus	B	0	14	−15	3.69	0.16	0.00011
hippocampus	L	−19	−20	−15	4.82	0.16	0.000012
hippocampus	R	15	−33	−5	4.11	0.16	0.000094
superior temporal gyrus	R	53	0	2	4.28	0.16	0.000061
superior temporal gyrus	L	−56	−20	9	3.52	0.16	0.00013
fusiform gyrus	L	−22	−47	−7	4.87	0.16	0.000099
Gray matter volume (GMV) corrected							
insula	L	−47	−5	4	3.82	0.41	0.00011
hippocampus	R	15	−33	−5	3.92	0.41	0.00015
hippocampus	L	−19	−20	−15	4.36	0.41	0.000048
superior temporal gyrus	R	53	0	2	3.98	0.41	0.00015
fusiform gyrus	L	−22	−47	−7	4.48	0.41	0.000033

MNI, Montreal Neurological Institute; B, bilateral; L, left; R, right;
*, false discovery rate (FDR)-corrected P values; Extent threshold k_E > 200 voxels

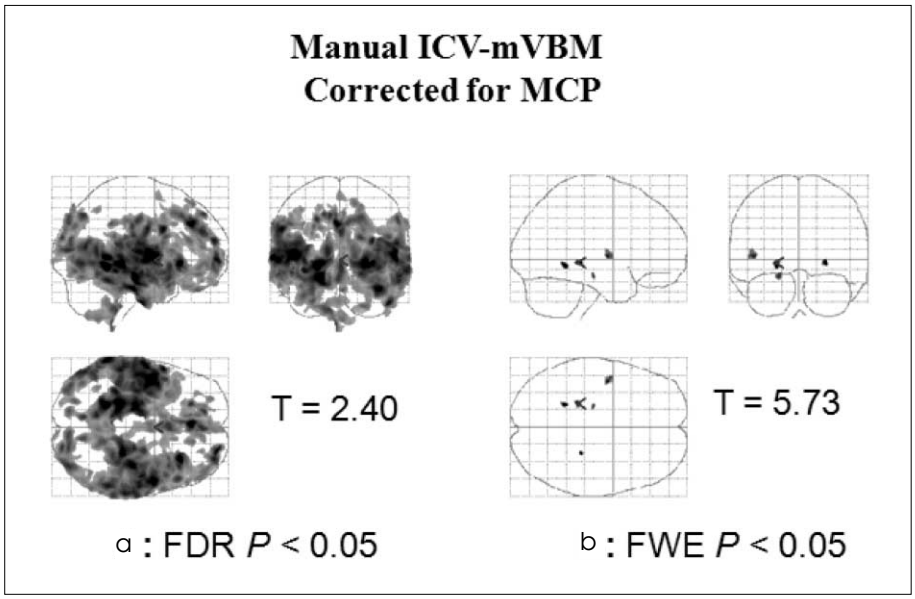

Fig. 4. Modulated VBM results after correction for multiple comparisons. The mVBM after manual ICV correction for the variability of individual maximum brain size showed significantly decreased GMV in MDD patients. FDR correction showed diffusively decreased GMV (a), and FWE correction, the most stringent correction, showed decreased GMC in the hippocampal and parahippocampal areas. However, the use of FreeSurfer ICV, the sum of gray and white matter volumes, or gray matter volume as confounders did not show any significant difference between groups after any correction method for multiple comparisons.

gyri, and fusiform gyri (Table 2, Fig. 3A). After correction by FreeSurfer ICV, reduced GMVC was demonstrated in the areas of the left superior frontal gyrus, right anterior insular cortex, left posterior insular cortex, bilateral gyri rectus, heads of the hippocampi, tails of the hippocampi, superior temporal gyri, and fusiform gyri. However, compared to the mVBM results corrected by manual ICV, no decreases in gray matter volume of the hypothalamus, parahippocampal gyri, or the body of the hippocampi were observed (Table 2, Fig. 3b).

The mVBM results corrected according to GWMV showed reduced GMVC in the right anterior insular cortex, left posterior insular cortex, bilateral gyri rectus, left head and tail of the hippocampus, the right tail of the hippocampus, bilateral superior temporal gyri, and left fusiform gyrus (Table 2, Fig. 3c). The mVBM results corrected according to gray matter volume showed reduced GMVC in the left insular cortex, left head and tail of the hippocampus, right tail of the hippocampus, right superior temporal gyrus, and left fusiform gyrus (Table 2, Fig. 3d). However, after correction for multiple comparisons, only the mVBM results corrected by manual ICV showed significant clusters for FDR or FWE correction, whereas the mVBM results corrected by FreeSurfer ICV, GWMV, and GMV did not show any significant cluster after FDR or FWE correction (Fig. 4).

Discussion

Manual ICV normalization provided the most sensitive results for both hippocampal volumetry in terms of detection of hippocampal atrophy and regional gray matter volume changes using mVBM, followed by the FreeSurfer ICV > GWMV > GMV correction methods. Moreover, GMV corrected by manual ICV decreased significantly in MDD patients, whereas other methods showed no effects. The results of this study suggested that the method of ICV measurement significantly affects the results of hippocampal volumetry and mVBM.

The estimation of premorbid brain size is essential in brain volumetric and morphometric studies in diseases characterized by brain atrophy (37). Because the skull grows along the suture lines and the maximum skull cavity is determined by brain expansion during normal growth, ICV measurements provide an estimate of maximum premorbid brain size and should be unaffected by atrophy due to neurodegeneration or aging (3), whereas cerebral volume may be significantly affected by neuropsychiatric disease and aging (2).

Although ICV obtained from T2-weighted MRI is generally used to estimate premorbid brain size in volumetric imaging studies, T1-weighted MRI can also be used successfully to estimate ICV (30, 37). Based on

the anatomical guidance of a previous study (30) and modified image preprocessing (31), it was possible to successfully estimate ICV with high reproducibility ($p = 0.996$) within 20 min per subject.

Various automated ICV measurement methods have been developed and used successfully, but discrepancies remain between manual and automated ICV measurement results (32, 37, 38). As far as the authors know, no studies have examined the normalization effects of ICV measurement methods on volumetric or morphometric analyses. Moreover, no previous study has compared ICV normalization effects in normal and atrophic brains.

In the present study, mean ICV (% difference, 0.83%) was similar between manual and FreeSurfer methods in the normal brain, but the mean FreeSurfer ICV was smaller than the mean manual ICV in MDD brain (% difference, 4.67%), and this difference markedly reduced the sensitivities of volumetric and mVBM analyses when used as a confounding factor in statistical analysis. The ICV underestimation of FreeSurfer in MDD patients could come from the inaccurate registration process determining ASF and the mask volume was not representative for the individual intracranial cavity (32).

In this study, premorbid ICV was similar between healthy subjects and chronic MDD patients, but total GMV corrected by manual ICV in chronic MDD patients was smaller than the GMV of normal subjects (Table 1). Our results suggest that gray matter, but not ICV, was affected by MDD, and these results support the previous hypothesis that, in contrast to brain volume, ICV does not vary over time (2).

Hippocampal damage has also been reported in MDD patients. Total and posterior hippocampal volume reduction without volume reduction of the anterior hippocampus was reported in unmedicated and remitted MDD patients (39). Furthermore, the right hippocampi of elderly depressed patients showed progressive volume reduction in a longitudinal study of hippocampal volume, and hippocampal volume reduction was correlated with memory deficits at 6 months (40). Another study indicated that decreased hippocampal volumes in MDD patients were correlated with poorer performance in the Wisconsin Card Sorting Test (WCST) (41). A recent meta-analysis of MRI studies concluded that hippocampal volume is reduced in MDD patients, but not in those with bipolar depressive disorder (42). In this study, hippocampal atrophy was demonstrated after volume correction by manual ICV, but no differences in hippocampal volume were observed after correction by FreeSurfer ICV, GWMV, or GMV. Because hippocampal volume reduction in depression has been repeatedly reported in a number of previous studies (37–42), and the patients enrolled in this study were chronic MDD, the finding of hippocampal atrophy is not surprising. So our results suggest that manually measured ICV, rather than FreeSurfer ICV or brain parenchymal volume, is the most reliable method to normalize hippocampal volume.

Conclusion

Our results indicate that mVBM analysis and hippocampal volumetry with manual ICV correction are more sensitive than the same analyses corrected by FreeSurfer ICV, GWMV, or GMV measurements. ICVs measured by FreeSurfer were underestimated in the MDD patients with atrophic brain. Therefore, it is recommended that more accurate methods for ICV measurement be used in brain volumetry and mVBM studies to estimate premorbid brain size. These results may also provide useful information regarding shape and cortical thickness analyses.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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두개강의 용적측정법이 해마의 용적측정술과 화소기반 형태계측술에 미치는 영향

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배경: 두개강내 용적에 대한 수동과 자동 측정법이 여성 주요 우울증 환자의 해마의 용적측정술과 modulated voxel-based morphometry (mVBM)의 결과에 미치는 영향을 알아보고자 한다.
방법: 21명의 여성 주요 우울증 환자와 성별, 나이의 분포가 비슷한 20명의 여성 정상인을 연구대상에 포함시켰다. 해마와 두개강내 용적은 수동으로 측정하였고, FreeSurfer 프로그램을 이용하여 두개강내 용적을 자동으로 측정하였다. 또한 회색질과 백색질의 부피도 SPM을 이용하여 자동으로 측정하였다.
결과: 수동으로 측정한 두개강의 용적을 통제변인으로 하여 분석한 통계분석의 결과가 FreeSurfer에 의해 측정된 두개강내 용적이나 뇌실질의 용적을 통제변인으로 한 통계분석의 결과보다 우울증 환자의 해마부피 감소와 mVBM 분석의 국조적 부피감소를 보다 민감하게 보여주었다. 수동적인 방법과 FreeSurfer에 의해 측정된 두개강내 용적은 정상인에서는 차이가 없었지만 ($p = 0.696$), 우울증 환자의 두개강 부피는 FreeSurfer를 이용해 측정한 두개강의 부피가 더 작았다 ($p = 0.000002$). 우울증 환자의 전체 회색질의 부피는 수동으로 측정한 두개강의 용적을 통제변인으로 적용하였을 때 정상인의 회색질의 부피보다 작았고 ($p = 0.000002$), 해마의 부피도 수동으로 측정한 두개강의 부피를 통제변인으로 통계처리를 했을 때는 우울증환자의 해마가 뚜렷한 위축을 보였지만 (오른쪽, $p = 0.014$; 왼쪽, $p = 0.004$), 다른 측정법을 통제변인으로 했을 때는 유의하지 않았다 ($p > 0.05$). mVBM 분석에서는 수동으로 측정한 두개강의 부피를 통제변인으로 사용했을 때만 다중비교교정 후에 유의한 결과를 보였다 (FDR $p < 0.05$).
결론: 수동적인 방법으로 측정한 두개강의 용적이 FreeSurfer에 의해 자동으로 측정된 두개강의 용적이나 뇌실질의 부피보다 해마용적측정술과 mVBM 의 결과에 있어서 더 효율적으로 우울증이 있는 그룹과 없는 그룹의 차이를 보여주는 것에 민감한 결과를 보였다.

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