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Development of a Group-specific Average Brain Atlas: A Comparison Study between Korean and Occidental Groups

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Abstract: One of the most important roles of a brain atlas is providing a spatial reference system in which multiple images can be interpreted in a consistent way. The brain atlase based on Western populations such as the International Consortium for Brain Mapping's 452 T-1 Weighted Average Atlas was widely used; however, they may not be the optimal choice for use with brain images from other ethnic groups, because structural differences between occidental and oriental brains have been reported. Therefore, in this study, we created an average brain atlas from 100 healthy Koreans (100 cases (M/F=53/47), 39.0 ± 17.0 years). The purpose of this study was to make a Korean average-brain atlas and to measure its differences from a widely accepted average brain atlas built on an occidental population. The average brain atlas for Koreans was developed using widely accepted tools and procedures. The comparison between the Korean and occidental averages was performed using tissue probability maps and a registration tool, and it was shown that the global pattern of differences between the two average brains found in this work agreed with previously reported differences: Korean brains are wider and shorter in size, and smaller in volume, yet no hemispheric volume asymmetry was found.

Key words: MRI, Korean, Group-specific brain atlas, Registration

INTRODUCTION

A brain atlas is a reference system where multiple brains are interpreted in a consistent way, whether they represent structural or functional information. It is especially useful for research that involves processing of multiple brain images to enhance the signal-to-noise ratio of an averaged image [1]. This processing requires the images to be aligned in a consistent space so that statistical consistency can be kept for the whole process; however, not all images in one study are guaranteed to have the same coordinate system, spatial alignment, and resolution. Consequently, a structural framework, in which individual brain images can be integrated, is needed so that the images are able to be analyzed in a quantitative manner [2].

In their early stages, structural brain atlases were usually obtained from a single postmortem specimen to describe anatomical features or relative positions of brain substructures [3, 4]. The limitation of these atlases is that a postmortem brain undergoes severe deformation caused by handing of the brain (freezing, extraction and slicing) that they are not appropriate for in vivo brain studies [5, 6]. With recent advances in Magnetic Resonance Imaging (MRI) technology, and improvement in data processing capacity, brain atlases based on multiple *in vivo* MR images began to emerge [1, 7, 8]. One of the most widely used average brain atlases was developed by the Montreal Neurological Institute (MNI) [7]. Three hundred and five MR images of healthy volunteers were registered into stereotaxic space using 9-parameter linear transformation. A more sophisticated average brain atlas was presented by the International Consortium for Brain Mapping (ICBM) [8]. Datasets from more than 7000 subjects were collected from the international members of the consortium, and 452 MR images of young adults were selected from the database to make an average brain atlas (ICBM_452, http://www.loni.ucla.edu/ICBM/ICBM_ICBMAtlases.html).

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While various types of brain atlases have already been developed, most of them are based on occidental brain images. These atlases may not provide an optimal reference system for processing brain images from other ethnic groups as structural differences between different ethnic groups have been reported [9-11]. Accordingly, it is favorable to have a group-specific—i.e., ethnic, gender, age, or disease—average atlas based on the images that are intended to be used with the atlas itself. This led us to develop our own average brain atlas specific to Koreans.

One important application of a group-specific brain atlas can be found in recent functional brain studies. In many cases, the results of functional or multi-modal brain studies, such as localization of activation sites, distribution of neurotransmitters, and white matter tractography, are associated with brain atlases to analyze or explain their mechanism with anatomical reference. Therefore, functional brain studies require not only consistent spatial reference, but also precisely standardized anatomical information of the group data. Karas et al. [12] suggested that a group-specific (or study-specific) average atlas was needed for optimized volume-based morphometry using Statistical Parametric Mapping (SPM, Institute of Neurology, University College of London, UK) program [13] to give more exact results because Alzheimer's disease patients have different brain structures than do controls. A similar problem that occurs when brain structures are too different from those of template images was also pointed out by a group of Korean researchers [14]. To allay this adverse effect, Kang *et al.* used a study-specific MR image from the subject group as a spatial reference, instead of the widely used occidental average atlas, MNI's 305 average template. The result was well understood with a study-specific average template but not with an occidental average brain [15]. Another group of researchers evaluated the differences between anatomical locations of mismatch negativity (MMN) generators in 24 healthy Korean subjects using a realistic head model and Talairach coordinate system [16]. They found that 62.5% of subjects showed different anatomical locations of MMN generators in both hemispheres in the realistic model and in Talairach coordinate. This study shows that an inappropriate use of a brain template may give misleading interpretation of functional brain study results. Therefore, it is important to have a group-specific average brain atlas to get more precise insight into the mechanisms of the human brain from the results of functional brain studies.

In this study, we developed an average brain atlas from the MR images of 100 healthy Koreans (Korean_100). The process of initial target selection and multiple steps of registrations were used to reduce bias due to using an individual image as a registration target. All procedures were carefully designed and adopted in order allow their use in making other group-specific brain atlases. We also compared the Korean_100 with the ICBM_452 in a quantitative way to investigate ethnic differences.

MATERIALS AND METHODS

Acquisition

This study was carried out under the guidelines for the use of human subjects established by the institutional review board of Seoul National University Hospital, Seoul, Korea. After being provided with a complete description of the scope of the study, written informed consent was obtained from all subjects. The study group consisted of 100 healthy volunteers who were recruited from the local community through the Health Promotion Center at Seoul National University Hospital or newspaper advertisements and were screened with the Korean version of modified Mini-Mental State Exam, Mood Evaluation Scale and a simplified version of the handedness testing [17, 18]. All subjects (20–70 years old) were matched for handedness and socio-economic status (Table 1). MR images were acquired on a 1.5-Tesla GE SIGNA Scanner (GE Medical System, Milwaukee, USA) using a 3D-SPGR T1-weighted spoiled gradient echo pulse sequence with the following parameters: 1.5 mm sagittal slices; echo time = 5.5 ms; repetition time = 14.4 ms; number of excitations = 1; rotation angle = 20°; field of view = 21 × 21 cm; matrix = 256 × 256.

Table 1. Description of the data of the 100 healthy Koreans used in this study

Gender	Number of Subjects	Age ($mean \pm SD$) (min: 20, max: 70)	Median age
Male	53	38.1 ± 16.8	28
Female	47	40.2 ± 18.0	32
Total	100	39.0 ± 17.0	30

Preprocessing

All images were resampled to an isocubic voxel (0.82 mm3) and realigned so that the anterior-posterior axis of the brain was aligned parallel to the inter-commissural line and the other two axes were aligned along the inter-hemispheric fissure [18]. The data sets were then filtered using anisotropic diffusion methods to improve the signal-to-noise ratio. These procedures were processed using commercial software—ANALYZE 4.0 (Mayo Clinic, Rochester, Minnesota, USA). For the tissues exterior to the brain, such as the skull and dural venous sinuses, the voxels were removed from all of the structural MR volume images using a semi-automated region growing method to enable extraction of the cerebellum [19].

Registration

The Procedure

In this study, Automated Image Registration program (AIR, version 5.2.5) was used for the linear and non-linear registration [20, 21]. The basic procedure was derived from the "AIR Make Atlas" pipeline [22]. All images were affined to a single subject and the transforms acquired during the affine transformations were averaged to form a "least distance space" into which every subject was be transformed and averaged. Then every subject was affined to the average and averaged again to form a linearly defined atlas. Finally, all images were warped (fifth order polynomial transformation) into the linear atlas and averaged to form the final atlas. This procedure is described in the following paragraphs since there were some modifications to the original procedure as well as adjustment of parameters (Fig. 1).

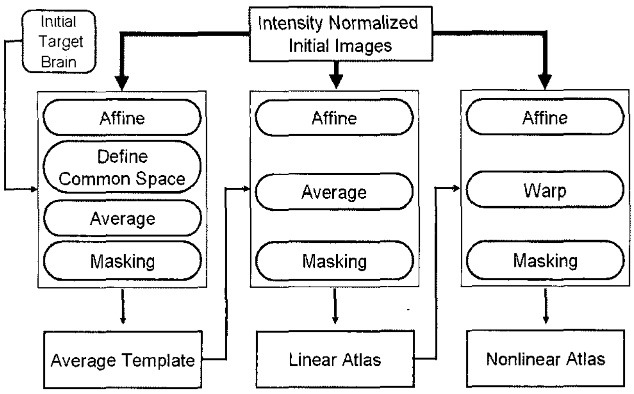


Fig. 1. The procedure for making the Korean_100 Atlas
The thick arrows indicate the flow of 100 images while the narrow lines mean a single image. The whole procedure consisted of three steps. First, the averaged template (AVT) was constructed to be used as a *bias-free* registration target. Then, linear registration was done based on the AVT for global scaling and linear alignment. Finally, non-linear fifth order polynomial warping was done to reduce natural variations caused by non-rigidity of the brains *in vivo*.

Cost Function

Among several cost functions available in AIR, the ratio intensity uniformity (RIU) was used as it attained stable and superior performance under various circumstances [21]. Another reason for using RIU was that the registration between an average MR image and an individual MR image should be regarded as inter-modality registration because their intensity relation is not as strong as between individual images.

Parameters

For linear registration, the options used were as follows: model = 3D 12-parameter affine transform; threshold = 0; convergence level = 0.00001; sampling = 180-to-1-voxel interval with a 3-voxel decrement per iteration; iterations = 25 per sampling; iteration stop condition = 5 times without improvement. Note that a predefined threshold value was used for defining outside of the brain. For non-linear registration, parameters were as follows: model = 3D fifth order polynomial warping; sampling = 81-to-9-voxel interval with a 3-voxel decrement per iteration; iterations = 50 per sampling. All other parameters were set to defaults. In addition, our running version of AIR was compiled for 8-bit MR images, with all other options for compilation set to default.

Intensity Correction

Making an average atlas involves intensity averaging of multiple MR images, which are susceptible to extrinsic noise that could affect the intensity distribution [23]. Therefore, intensity normalization was done before any processing of volume images to guarantee appropriate mapping of the same tissue classes from different images onto a specific intensity range. The target for intensity normalization was the same volume used for the initial target. The target volume was intensity-adjusted to its full intensity scale (0–255) before skull extraction. The normalization coefficient was found by an intensity normalization program, inormalize, which was originally a part of the Brain Imaging Software Toolbox (Brain Imaging Center, Montreal Neurological Institute, McGill University, Canada) [24].

The Initial Target Brain: The Selection of a Representative Subject

The method for finding an optimal registration target within a group of images was thoroughly studied by Kochunov et al. [25, 26]. With the same purpose, we used a similar but rather simple method to find the registration target with minimum deformation in the group.

First, all images were transformed into Talairach space. Then, we defined eleven characteristic vectors (CV) in the Talairach space using anterior commissure, posterior commissure (AC, PC) points, and the boundary of the cortical surface. These CVs were calculated for each image and averaged to form a group-specific average vector (AV) (Fig. 2). The definitions of the vectors are as follows:

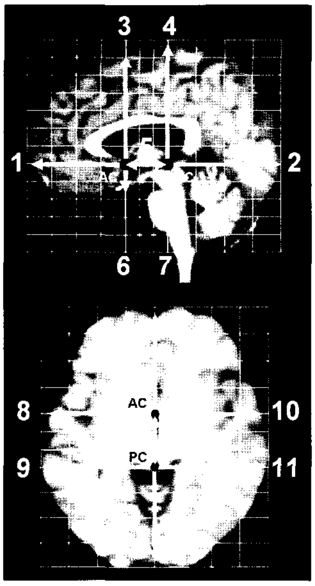


Fig. 2. Definition of the 11 basis vectors those were used in the selection of the initial target brain
(1) anterior boundary–AC; (2) posterior boundary–PC; (5) AC–PC; (3, 4, 6, 7) AC/PC–superior/inferior boundary; (8, 10) AC–left/right horizontal boundary; and (9, 11) PC–left/right horizontal

$$CV_i = (cv_{i1},\ \ldots\ldots,\ cv_{ij})^T \quad (1)$$

$$AV = (av_1,\ \ldots\ldots,\ av_j)^T,\quad av_j = \frac{1}{M}\sum_i^M cv_{ij} \quad (2)$$

$$\begin{aligned} DV_i &= (av_1 - cv_{i1},\ \ldots\ldots,\ av_j - cv_{ij})^T \\ &= AV - CV_i \end{aligned} \quad (3)$$

where i is an image index and j is a vector index (N = 11 in this case and M is the total number of subjects images in a group). Finally, the brain image, i, with

$$i \leftarrow \min\|DV_i\| \quad (4)$$

was selected as the initial target brain (ITB). This brain image was screened by a neuroanatomist to check for abnormal deformation.

The Average Template and the Atlases

The whole process consists of three steps: making the average template (AVT), linear atlas (LINA), and non-linear atlas (NLINA, Fig. 1). First, to reduce variations of global alignment and scale, all initial volumes were affined to the ITB. The distances among the affined images were minimized [21], and the images were averaged. Then, the voxels of intensity under a pre-defined threshold on the brain–non-brain boundary were masked out to form the AVT.

To avoid the following registration procedure from being biased by using an individual image as a registration target, the AVT was used as the registration target for the LINA. Then, all intensity-normalized initial volumes were affined to the AVT, averaged and masked again, yielding the LINA. Finally, all volumes were affined, and warped onto the LINA, followed by averaging and masking. This final average volume is the NLINA, and for this step, non-rigidity of the brain was considered: non-linear fifth order polynomial warping was used. This gave the Korean Average Brain Atlas, Korean_100.

The Comparison

Both the Korean_100 and the ICBM_452 were realigned by setting AC-PC vector to horizontal. Then, Korean_100 was registered (3 rotation, 3 translation rigid body transformation) onto the ICBM_452 to preserve its original characteristics in size and volume (Fig. 3). After that, the size of the bounding boxes and total volume were measured. Another way of measuring an average atlas is to use tissue probability maps (TPMs, Fig. 4) [27]. Since both TPMs of Korean and ICBM are in the same space as their own average brain atlases are, they can be used for counting the probabilistic volume of the average atlas. No segmentation errors or partial volume effects are introduced when measuring volume in TPMs although the localization of volume differences is not possible. It should be kept in mind that the absolute values cannot be directly compared with each other when measuring averaged images. Therefore, the ratios of volume or size were also calculated for the comparison.

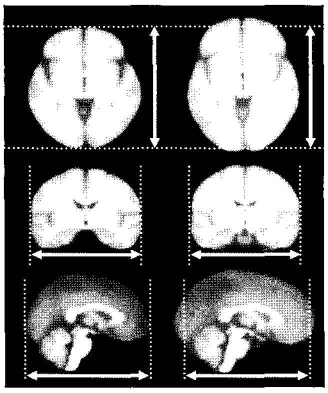
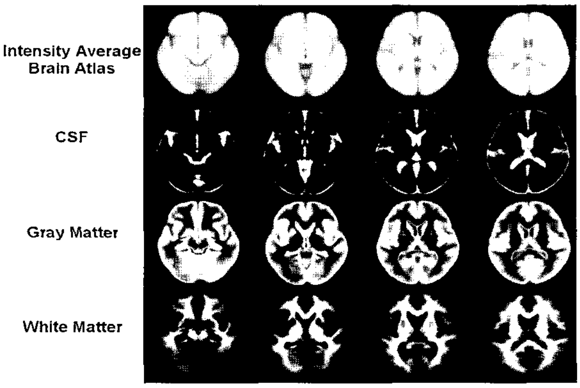
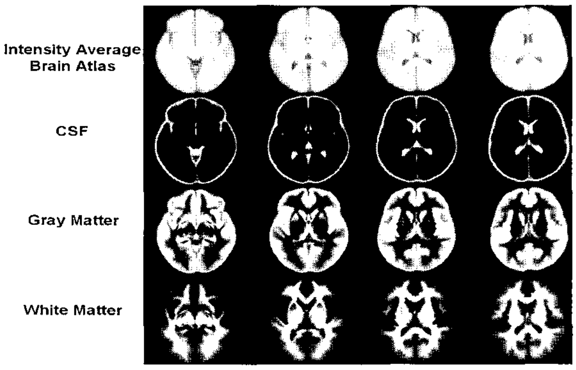


Fig. 3. Difference between the average brain atlas used in this study (left column) and the ICBM 452 T1 atlas (right column) Rigid body transform (6 parameters) was applied to align two different spatial coordinates. As regards ethnic differences, our atlas based on oriental populations is relatively shorter but wider than ICBM atlas based on occidental brains.



(a) Korean



b) ICBM

Fig. 4. The tissue probability maps of the Korean and ICBM used to measure the volume
The tissue probability map was built with the transformation matrixes obtained by registering (affine and warping) initial volumes to the non-linear atlas. After acquiring the transformations, each set of segmented white matter, gray matter, and cerebrospinal fluid images were re-sliced and averaged to form the probability map for each tissue class.

RESULTS

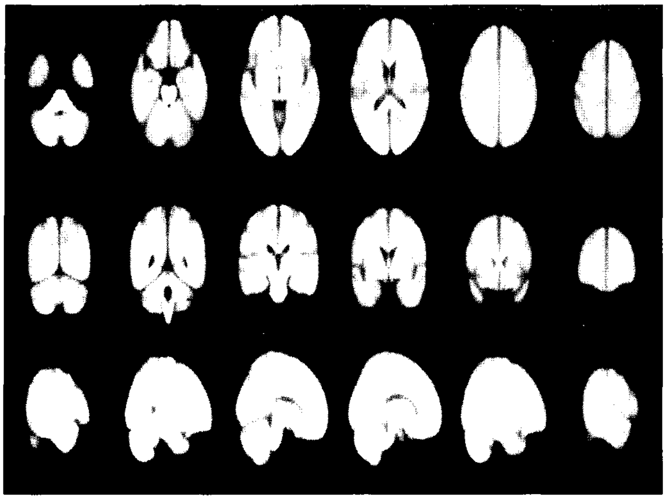
Our atlas based on Korean populations is relatively shorter but wider than the ICBM atlas based on occidental ones (Table 2, Fig. 5). Therefore, our results confirm the previously reported differences between occidental and oriental brains [11]. Note that the length/width ratio of the Korean_100 (1.15) is closer to 1 than that of the ICBM_452 (1.30): the bounding box of the Korean_100 brain is closer to a cubic square.

Volume measurement was performed using the TPMs of both atlases (Table 2). The Korean_100 was smaller in volume while maintaining a GM/WM ratio (1.30) very close to previous reports [28, 29]. In addition, hemispheric L/R volume asymmetry was calculated. The asymmetry index was given as 2 × (L – R)/ (L + R), where L and R were measurements for the left and right hemispheres. The symmetry range was established between the index values –0.1 and +0.1 [30, 31]. Asymmetrical cases were those showing values below –0.1 (right-sided pattern) or above +0.1 (left-sided pattern). The asymmetry indices were –0.021 for ICBM_452 and –0.016 for Korean_100. Therefore, no asymmetry was found in both the Korean and ICBM average atlases, as described in previous literature [10].

Table 2. Comparison between the Korean and ICBM average brain atlases
As for the ethnic differences, our atlas based on oriental populations is relatively shorter but wider than the ICBM atlas based on occidental brains. In addition, the volume ratio of GM and WM was measured in tissue probability maps (TPMs), to reduce the partial volume effect. Note that the ratio of GM/WM is very close to previous reports while the Korean atlas tends to be smaller in volume than the ICBM's.

Measurement	Korean_100	ICBM_452
Bounding Box Size		
Width (mm)	139	135
Length (mm)	160	176
Ratio (length/width)	1.15	1.30
Volume		
GM/WM ratio	1.36	1.30
Total Volume (cc)	1467.07	1594.17
Ratio (ICBM/KOREAN)	1.09	

Note: Rigid body transform (6 parameters) was applied to align two different spatial coordinates. Actual comparison should be made in the ratios, due to the effect of multiple steps of registrations and masking, although it was measured in metric units.



(a) Korean

(b) ICBM

Fig. 5. The Korean vs. ICBM Average Brain Atlas
Our average brain atlas is based on 100 subjects, which is a relatively small number compared with the ICBM's, yet it shows quite reasonable resolution, sufficient to show important anatomic details.

DISCUSSION AND CONCLUSION

Selection of an Initial Target for Registration

Techniques for choosing optimal targets for registration have been devised by several researchers [21, 25, 26]. In this paper, we used a simple averaging technique to define registration targets. Although using an average template rather than an optimized individual target brain [25] degrades the sharpness of the average atlas, it is still meaningful in that an averaging significantly reduces the influence of a single brain on the subsequent registration process, thereby allowing the atlases to be less biased while more precisely representing the whole group of images.

Registration Failures

During the linear registration, we encountered several cases of registration failures with default parameters of AIR. These misregistrations significantly degraded the quality of the final average image; therefore, all registration results were visually inspected. This problem occurred because our data had different intensity distribution and morphological characteristics than the occidental data used in developing AIR. Therefore, it is recommended that the registration parameters should be adjusted heuristically when they are used on new data for the first time. Once the parameters that work well with a new dataset are found, there is no need of visual inspection as long as the characteristics of the data are unchanged.

Subject Deficiency and Population Representativity

Our brain atlas is based on 100 subjects, which may not be enough of our target group—the entire Korean population. ICBM's atlas is based on 452 subjects who were chosen from a database with more than 7000 subjects. MNI's atlas used 305 subjects, which is still a large number considering that it was made in the early 1990s. Although it is not certain how many subjects are needed to build an average brain atlas, we have reasonable amount of data to observe global pattern of group differences. However, more subjects are needed considering the aging effect over the subjects' age varying 20 to 70. In addition, having sufficient subjects will give us flexibility in building brain atlases targeted to other characteristics because it then becomes easier to build subsamples of the whole population based on different characteristics.

The Pattern of Structural Differences

Zilles *et al.* reported that Japanese brains are relatively shorter but wider than European brains [11]. They also presented that inter-subject, gender, and ethnic differences exist between brains, and confirmed distinct patterns of differences in a statistically meaningful way. Our result shows a similar pattern of Korean brains being shorter and wider than occidental brains.

Summary and Conclusion

We have demonstrated a method for developing a group-specific average brain atlas. By implementing multiple steps of registration, the average brain atlas was relatively less biased once a registration target was created, thereby removing the effect of structural variations among subjects that originate from natural causes. A comparison between the Korean average brain atlas and ICBM 452 T-1 average atlas was performed, and it was shown that ethnic differences exist between Korean and occidental brains, as described in the published literatures [9-11].

It is important to have a group-specific brain atlas for multi-subject brain research, whether structural or functional. Although only ethnic-group-specific brain atlases were studied here, further research on other characteristics such as gender, age, and disease should be done to provide optimal atlases for relative study topics. In addition, these group-specific atlases can replace the template images that are currently provided with research tools. For instance, SPM is currently being distributed with MNI's average brain. It is possible to enhance the accuracy of research results by exchanging this occidental brain template with a study-specific brain atlas, as there are structural differences between groups of populations. Therefore, it is necessary to make and distribute various group-specific brain atlases in the future.

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