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3차원 MR 영상으로부터의 한국인 뇌조직확률지도 개발

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Development of Korean Tissue Probability Map from 3D Magnetic Resonance Images

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요 약 : 대뇌 조직 구분을 위한 선험적인 정보를 제공하기 위한 뇌 조직 확률 지도를 개발하는 경우 개인마다 구조적으로 다양한 형태를 가진 뇌의 특성과 특히 인종간의 두드러진 차이를 반드시 고려해야 한다. 본 연구에서는 특정 그룹에 대한 뇌 조직 확률 지도를 제작하는 데 필요한 절차를 알아보고 나이에 따른 그룹 간의 뇌 조직 확률 지도의 구조적인 차이를 살펴보고자 한다. 피험자 그룹은 100명의 건강한 한국인이며 나이에 따라 두 그룹으로 분류하였다. 뇌 확률 지도의 기준 좌표계를 설정하기 위해 전체 그룹 내의 모든 피험자의 뇌 영상에 대한 평균 영상을 구하고, 각 뇌 영상을 기준 좌표계로 정규화 시킨다. 정규화 과정에서 얻어진 변환 매개 변수를 미리 각 뇌 조직(회질, 백질, 뇌척수액)으로 분할된 피험자의 영상에 적용하고 각 그룹 내에서 변환된 뇌 조직 영상을 평균함으로써 뇌 조직 확률 지도를 완성하였다. 나이에 따른 구조적인 차이를 살펴보기 위해 그룹 간 확률 값의 차이 영상을 구하였다. 이전 연구결과에서와 마찬가지로 나이가 증가함에 따라 뇌실이 확대되고 회질의 위축이 전체적인 뇌 영역에서 일어났다. 그러므로 우리는 대뇌 조직 분할을 위해 선험적인 정보들을 사용하고자 할 때는 특정 그룹에 대한 뇌 확률 지도를 사용할 것을 제안한다.

Abstract : The development of group-specific tissue probability maps (TPM) provides a priori knowledge for better result of cerebral tissue classification with regard to the inter-ethnic differences of inter-subject variability. We present sequential procedures of group-specific TPM and evaluate the age effects in the structural differences of TPM. We investigated 100 healthy volunteers with high resolution MRI scanning. The subjects were classified into young (60, 25.92±4.58) and old groups (40, 58.83±8.10) according to the age. To avoid any bias from random selected single subject and improve registration robustness, average atlas as target for TPM was constructed from skull-stripped whole data using linear and nonlinear registration of AIR. Each subject was segmented into binary images of gray matter, white matter, and cerebrospinal fluid using fuzzy clustering and normalized into the space of average atlas. The probability images were the means of these binary images, and contained values in the range of zero to one. A TPM of a given tissue is a spatial probability distribution representing a certain subject population. In the spatial distribution of tissue probability according to the threshold of probability, the old group exhibited enlarged ventricles and overall GM atrophy as age-specific changes, compared to the young group. Our results are generally consistent with the few published studies on age differences in the brain morphology. The more similar the morphology of the subject is to the average of the population represented by the TPM, the better the entire classification procedure should work. Therefore, we suggest that group-specific TPM should be used as a priori information for the cerebral tissue classification.
Key words : Tissue Classification, Average Atlas, Tissue Probability Map, Age Effect, Magnetic Resonance Image

INTRODUCTION

Probabilistic approach has been existed in large numbers as a research strategy and clinical studies for generating anatomical templates, expert diagnostic systems, and knowledge-based imaging tools that retain quantitative information on inter-subject variations of brain architecture in neuroanatomy study [1-3]. The existing studies are showed up as follow. In case of anatomical based geometric brain tissue probability models have been used as *a priori* information for the automated tissue classification [4-9]. Also, probability maps can provide key information for functional neuroanatomical studies. Tomaiuolo et al. applied the probability map of the pars opercularis of the inferior

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frontal gyrus in functional study of language [10]. Momenan et al. described a voxel-based method for quantitatively assessing the homogeneity of tissues from structural images of groups, which supplemented functional data analysis, indicating the structural or tissue homogeneity of the areas of significant functional activations [11]. A stereotaxic space tissue probability map (TPM) of a given tissue is a spatial probability distribution representing a certain subject population. Prastawa et al. generated spatial prior probability images for the tumor and edema from the difference of the T1 post-contrast and the T1 pre-contrast images [9]. The decision of lesion was made by analysis of the probability map of white matter in a point of view of clinical studies utility [12,13].

As described above, spatial probability distribution for each tissue provided by TPM can be used to automatically produce a training set for the supervised classifier. Nevertheless, the particular TPM used is not a critical factor in tissue classification but just an initial guess for the algorithm. However, the more similar the morphology of the subject is to the average of the population represented by the TPM, the better the entire classification procedure should work [14]. The recent studies presented the considerable degree of variability in hemispheric shape between individuals, gender and age as well as ethnic groups [15,16].

A number of tissue probability maps have been presented from various research groups. International Consortium for Brain Mapping (ICBM) provided tissue probabilistic atlases of 452 subjects [17]. The probability images used as a prior knowledge in SPM software and provided by the Montreal Neurological Institute were derived from scans of 152 young subjects [18]. However, since inter-ethnic differences of inter-subject variability were present, Korean-specific tissue probability map (KTPM) had been needed for domestic neuroimage analysis [16]. In this study, we propose the sequential procedures of group-specific TPM construction and evaluate the effects of age in the structural differences of TPM.

METHOD

A. Subjects and Data Processing

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. After being provided with a complete description of the scope of the study, written informed consent was obtained from all of the subjects. The study group consisted of 100 healthy volunteers who were recruited from the community through newspaper advertisements and were screened by neuro psychological test [19]. Demographic characteristics of subjects are summarized in Table 1. MR images was acquired on a 1.5T 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.

Following the methods of our previous study, images were resampled to isocubic (0.82 mm^3) 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 [19]. The data sets were then filtered using 2D affine anisotropic diffusion filtering to improve the signal-to-noise ratio. These procedures were processed using the commercial software-ANALYZE 4.0 (Mayo Foundation, USA). Non-brain tissues were removed by the modified region growing method. And then, we applied morphological operations to the extracted cerebral image in order to restore approximately the outer cerebrospinal fluid (CSF) only in the sulcus, not gyrus. These operations consisted of sequential dilation, which is used to expand the image, and erosion, which is used to shrink it. The extracted cerebral images were classified into gray matter(GM), white matter(WM) and CSF, employing the fuzzy clustering algorithm that was chosen because it did not require the use of a priori probability [20].

Table 1. Demographic characteristics of subjects

Group	Number of subjects	Age Distribution	Mean (SD)
Whole	100	20 ~ 70	39.00 (17.00)
Young	60	20 ~ 40	25.91 (4.58)
Male	33	20 ~ 38	25.94 (4.55)
Female	27	20 ~ 40	25.89 (4.70)
Old	40	41 ~ 70	58.83 (8.10)
Male	20	41 ~ 69	58.10 (7.99)
Female	20	41 ~ 70	59.55 (8.36)

B. Spatial Normalization to the intensity average brain atlas

The intensity average brain atlas was derived from skull-stripped images of the same population used in this study to avoid any bias from random selected single subject and selected as the target of TPM. The whole process was performed on *IBM Linux Cluster 1350* (8 nodes, 2GHz Intel Zeon CPU, 8GB RAM) using *AIR 5.2.5* [17,21,22]. The procedures of creating the atlas consist of three steps. All data are affine transformed into the random selected single subject as a target brain and averaged base on intensity [Fig.1 (a)]. Then, all the subjects are realigned with affine transformations to the average template and again averaged to form a linearly defined atlas in both intensity and spatial domains [Fig.1 (b)]. A final step is a fifth order polynomial

nonlinear alignment to the atlas space for each subject. Each subject is transformed into the linearly defined atlas space and averaged to form the final atlas [Fig.1 (c)].

The transformation parameters of initial classified images, such as affine matrix and fifth polynomial coefficients, were derived from the transformation of each subject to the previously constructed atlas.

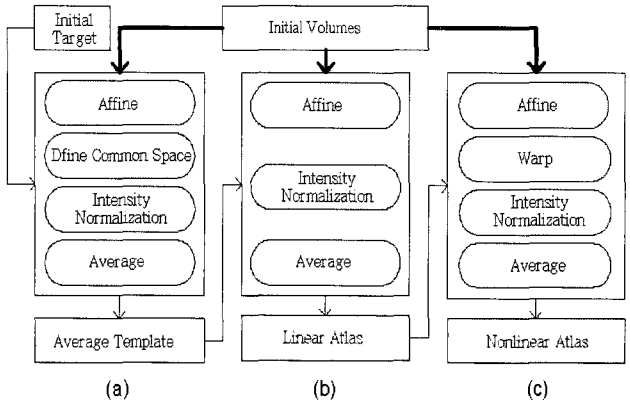


Fig. 1. The flowchart of the intensity average brain atlas (a) Average template: Initial volumes were affined to a randomly selected image (initial target). (b) Linear atlas: All initial volumes were affined to the average template and averaged again (c) Nonlinear atlas: It is made up of affine and a fifth order polynomial alignment to the linear atlas. This is the target of spatial normalization for tissue probability map.

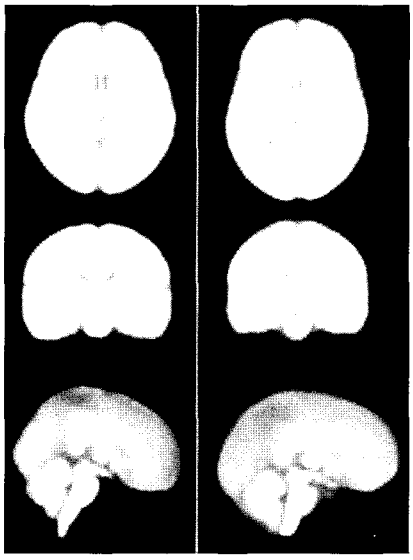
C. Construction of Tissue Probability Maps

The tissue-classified volumes were averaged to create the TPM with each voxel corresponding to a coordinate in the intensity average brain atlas. The probability value of GM, WM and CSF are stored at each voxel where tissue probability was defined as the fraction of times that had the voxel classified as that tissue. Probability value of each voxel is combined equal to one. The group-specific TPM of each subpopulation was constructed and evaluated age effects in structural differences of probability distribution. Two calculations were performed on all tissue probability images: young > old, and old < young. To account for different image contrasts due to different field strengths, field inhomogeneities, etc, results were only considered valid if the tissue probability difference was found to be larger than 20% [23].

RESULT

A. Average Brain Atlas as Target of Tissue Probability Map

The intensity average brain atlas was used as the target of spatial normalization for TPM. Although it is difficult to validate the average brain atlas, we provide the ICBM 452 T1 atlas, which is widely used in brain mapping community, for the comparison with our results (http://www.loni.ucla.edu/ICBM/ICBM_452-T1.html, Fig. 2).The average brain atlas used in this study is relatively shorter, but wider than ICBM 452 atlas. It is consistent with the ethnical differences of hemispheric shape, proposed by Zilles et al [16].

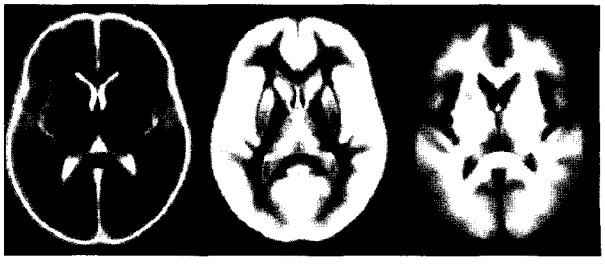


(a) (b)

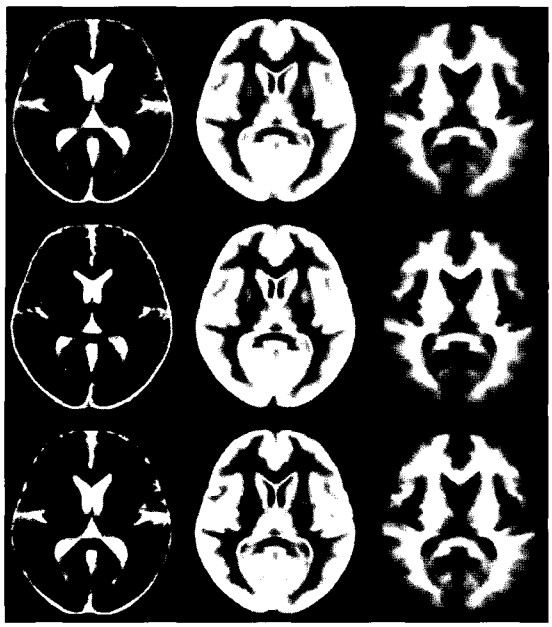
Fig. 2. The intensity average brain atlas for (a) The same population used in this study; (b) 452 subjects provided by ICBM, shown in transversal, coronal and sagittal sections (top to bottom). The average brain atlas used in this study is relatively shorter, but wider than ICBM 452 atlas.

B. Group-specific Tissue Probability Map

The skull-stripped image of each subject was spatially normalized to the intensity average brain atlas and transformation parameters were derived and applied to the classified image of each subject. The subjects were classified into young and old groups according to the age. The cross sections of TPM shown in Fig. 3 were obtained from three groups whole, young and elderly group. Although the global patterns of spatial probability distribution are similar to one another, there are remarkable differences between young and elderly groups. The TPM of old group shows relatively larger ventricle and thinner cortical region than young group.



(a)



(b)

Fig. 3. Tissue probability images for CSF, GM and WM (left to right). (a) 452 subjects provided by ICBM (b) The same population used in this study- top: Whole group (100 subjects, 20-70 years old); middle: young group (60, 20-40); bottom: old group (40, 41-70). Although the global patterns of spatial probability distribution are similar to one another, there are remarkable differences in ventricle CSF and cortical GM between young and old groups.

C. Age Effects in Spatial Distribution of Tissue Probability

The result of the two calculations, which is overlaid on the intensity average brain atlas, is shown in Fig. 4, with the color coding representing the direction of changes: blue denotes a higher tissue probability in the young group (young > old), while red signifies a higher tissue concentration in old group (old > young). The differences shown represent an at least 20% difference in tissue probability. The old group shows considerable cortical atrophy in the tissue probability image of GM and enlarged ventricle in that of CSF, compared with young group. Our results are generally consistent with the few published studies on aging effects in brain morphology [24,25].

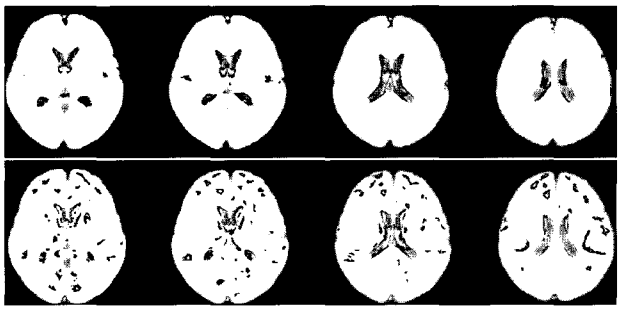


Fig. 4. Comparison of the group-specific tissue probability maps: young > old (blue), and young < old(red). Top: CSF , Bottom: GM. Results correspond to an at least 20% difference in tissue probability. (Minimum cluster size = 500 voxels)

DISCUSSION & CONCLUSION

This study describes the sequential procedures of group-specific TPM and evaluates the age effects in the structural differences of TPM. There are several limitations in this study. First, it is deficient in the amount of data set. Motivated by the vast amount of information that is rapidly accumulating about the human brain in digital form, ICBM embarked upon a program to develop a probabilistic atlas and collected data set that included 7000 subjects between the ages of 18 and 90 years [26]. Therefore, it is needed to supplement with additional subjects. Second, the quality of CSF probability map was inferior to one of the ICBM in contrast to the GM or WM (Fig.1). It resulted from the morphological approximation in the skull-stripping procedure. It is impossible to define exact cerebrum included entire CSF with one's eyes because the intensity of CSF in T1-weighted MRI is nearly similar to that of background. Moreover, the region between skull and cerebral cortex is not pure CSF but included other tissues- such as fat and dura mater, so it is difficult to extract cerebrum from brain image even though manual establishment of ROI. Although its quality will be improved if T2- and PD-weighted MRI are included, due to the resolution of image and costs, only T1-weighted MRI is used in the structural analysis on the brain except special cases- such as tumor identification. Finally, there has been sufficient method of evaluation for the probabilistic results, except the visual inspection. In general, binary segmentations of the probability map by applying different thresholds are compared with the gold standard, which is manual segmentation result by the anatomist, using similarity index [27,28]. In practice, the probability of voxels might be more useful than the binary segmentations and it is desirable to have a general measure for clarity of the evaluation, representing the accuracy of probability map as a whole. Therefore, it is needed to derive a probabilistic version of the similarity index or another measure.

A point view of brain atlas has a common space for whole data, using average atlas as the standard coordinate for probability map instead of a single brain as a target brain is objective and valid choice. A point of view visual inspection, comparison Korean atlas with ICBM atlas is different morphology and shape. The leading studies referred to the orient brains are relatively shorter, but wider than the occident brains [16]. Korean atlas is shown a poor quality at sub-cortical area comparison with ICBM altas. This problem will be solved collecting more subjects. Also, central to the probability map is the accuracy of registration and tissue classification, as well as an amount of data set.

Advancing age in humans is generally associated with

decreased brain tissue size and increased brain CSF volume [24,25]. Preliminary results are shown difference for the age, so in case of group studies is need to use suitable tissue probability map as a priori knowledge.

In conclusion, this study presents the procedure for group-specific TPM, especially Korean group. It will be used as a prior knowledge of tissue classification as well as a standard coordinate system of functional data in domestic neuroimage analysis. As described above 'Result' section, the intensity average brain atlas used in this study showed the ethnical differences of brain morphology and group-specific TPM exhibited aging effects in spatial distribution of tissue probability. The more similar the morphology of the subject is to the average of the population represented by the TPM, the better the entire classification procedure should work.

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