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# Fully-automated approach to hippocampus segmentation using a graph-cuts algorithm combined with atlas-based segmentation and morphological opening

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#### ABSTRACT

The hippocampus has been known to be an important structure as a biomarker for Alzheimer's disease (AD) and other neurological and psychiatric diseases. However, it requires accurate, robust and reproducible delineation of hippocampal structures. In this study, an automated hippocampal segmentation method based on a graph-cuts algorithm combined with atlas-based segmentation and morphological opening was proposed. First of all, the atlas-based segmentation was applied to define initial hippocampal region for a priori information on graph-cuts. The definition of initial seeds was further elaborated by incorporating estimation of partial volume probabilities at each voxel. Finally, morphological opening was applied to reduce false positive of the result processed by graph-cuts. In the experiments with twenty-seven healthy normal subjects, the proposed method showed more reliable results (similarity index =  $0.81 \pm 0.03$ ) than the conventional atlas-based segmentation method ( $0.72 \pm 0.04$ ). Also as for segmentation accuracy which is measured in terms of the ratios of false positive and false negative, the proposed method (precision =  $0.76 \pm 0.04$ , recall =  $0.86 \pm 0.05$ ) produced lower ratios than the conventional methods ( $0.73 \pm 0.05$ ,  $0.72 \pm 0.06$ ) demonstrating its plausibility for accurate, robust and reliable segmentation of hippocampus.

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#### 1. Introduction

Magnetic resonance imaging (MRI) of brain provides anatomical information on disease-related for detection of pathology and treatment planning. Its quantitative volumetric analysis is necessary to define anatomical structure thus playing an important role in the clinical research. The hippocampus has been known as one of the most important structures related to several neurological disorders, such as Alzheimer's disease (AD) [1], mild cognitive impairment [2], schizophrenia [3] and epilepsy [4]. In particular, the hippocampus was affected at the earliest stages of AD and thus used as a biomarker of early AD in several studies [5–7]. While accurate and reliable segmentation methods are crucially important for automatic delineation of hippocampus, it is relatively more difficult than with any other structures in brain [8]. Furthermore, superposition of several tissue types around the hippocampus is not always well resolved and a large part of its border with the amygdala is usually indistinguishable.

While manual segmentation [5,9] approaches have been widely used, they were handicapped especially in large-scale studies due to the intrinsic characteristics such as time-consumption and laborexpensiveness as well as inter- and intra-rater variability. On the other hand, semi-automated methods utilized a priori information such as user-defined landmarks [10–12]. Even though they reduced a certain amount of effort to delineate hippocampal region, they are still inappropriate to a large clinical study since determination of the initialization requires the time-cost and manual intervention. Then, several automated methods have been proposed as follows. The automated methods for segmenting hippocampus typically utilized the constraints such as optimization of cost function for the geometry and the anatomical object [13-15]. Joshi et al. [14] proposed a Bayesian deformable approach incorporating prior knowledge of the anatomical variations and the imaging modalities. Pizer et al. [15] used the *m*-rep model to provide prior geometric information effectively in deformable models segmentation approach. Even though these deformable model-based methods

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produced segmentation results of improved reproducibility, they are quite dependent on the initial conditions. Recently, a Bayesian statistical model of shape and appearance for subcortical segmentation was proposed and implemented as the freely-available package (*FIRST*, http://www.fmrib.ox.ac.uk/fsl/first/index.html) [16].

Another popular automated method is atlas-based segmentation. An individual datum is registered to the atlas space and the resulting transformation is used to propagate the atlas on which regions of interest have been manually defined by a neuro-anatomist. In atlasbased segmentation, its performance is fully dependent on the labeling of each region and registration algorithm. Recently, it has been combined with conventional segmentation algorithms such as, graph cuts or expectation maximization algorithms [17–19]. Similarly, Wolz et al. [18] applied a graph cuts algorithm to simultaneously measure hippocampal atrophy in longitudinal studies.

In this work, we proposed a fully automated method using graph cuts [20,21] combined with atlas-based segmentation and morphological opening, which is robust for anatomical variation between different subjects. It was applied to a healthy normal population who had manually defined hippocampal regions which could be used for the evaluation.

#### 2. Materials and methods

#### 2.1. Datasets

Three-dimensional T1-weighted MR images for this study were obtained from Samsung medical center, Seoul, South Korea. Acquisition parameters on the scanner (GE Signa, Milwaukee, WI) had echo time 4.59 ms, repetition time 9.878 ms, flip angle 8°, 360 slices of 0.5 mm thickness and matrix size 480 × 480 pixels. Twenty-seven healthy normal subjects (71.82  $\pm$  7.34 years old) took part in the study. We obtained informed consents from all participants and the study was approved by the institutional review board of the Samsung Medical Center.

Regarding the ground truth for validation of segmentation results, left and right hippocampal regions of all subjects were manually drawn on coronal slices using ITKSNAP 1.6 (www.itksnap. org). The hippocampal region was manually traced from the hippocampal head to the tail, including the cornu ammonis, dentate gyrus, subiculum, ambient gyrus, and the gyrus fasciolaris [22]. Two independent operators repeatedly drew hippocampal regions in three slices randomly selected from individual volume data to evaluate reliability of the manual delineation using the intra-class correlation coefficient (ICC) [23].

#### 2.2. Initialization with atlas-based segmentation

First of all, atlas-based segmentation was applied to define hippocampal region which would be used a priori information for the following graph cuts algorithm. A neurologist manually drew the hippocampal region on the International Consortium for Brain Mapping (ICBM) 152 symmetric template, which was delineated in the coronal view while the other views at the same position were displayed simultaneously. It would be used as the hippocampus atlas to define the hippocampal region from individual data using nonlinear registration.

The following pipeline image processing steps were applied for further analysis, as described in detail elsewhere [24–29]. At first, the native MRI data of all subjects were registered into the template using a linear transformation and corrected for intensity non-uniformity artifacts [29]. And then, an artificial neural network classifier [27] was applied to identify gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Finally, partial volume levels, MRI intensity-mixing at the tissue interfaces due to the finite resolution of the imaging device, were estimated and corrected using a trimmed minimum covariance determinant method [27,30]. Estimating the fractional amount of each tissue type within each voxel improved the accuracy of a priori information for graph cuts algorithm which would be explained later (See 'Graph cuts approach' section). A hierarchical multi-scale non-linear fitting algorithm (ANIMAL) [26] was then applied to obtain the 3D deformation vector field that maps the template onto the individual brain volume. And then the resulting vector field was used to transform the hippocampus atlas [31]. In addition, the component of WM or CSF from the transformed hippocampus atlas was masked out by GM-classified map of each subject in order to exclude the false positive for graph cuts algorithm.

#### 2.3. Graph cuts approach

A graph cuts algorithm is used to find a global minimum of energy function with minimum cut/maximum flow algorithms on graph [20,21]. A directed weighted graph  $G = \langle v, \varepsilon \rangle$  consists of a set of voxels v of the image and a set of edges  $\varepsilon$  between every neighboring voxel. The graph has two different types of edge such as N-links and T-links. An N-link is defined by the connection between neighboring voxels, and a T-link connects between an image voxel and one of two terminals which correspond to foreground and background. The boundary between foreground and background was obtained by finding the minimum cost cut on the graph *G*, which an energy function can be formulated as:

$$E(f) = \sum_{p \in P} D_p\left(f_p\right) + \sum_{\{p,q\} \in N} V_{p,q}\left(f_p, f_q\right)$$

where  $f = \{f_p \mid p \in P\}$  denotes a labeling of the image *P*, and  $D_p$  (·) is a unary term derived by cost on the edges of T-links'. And  $V_{p,q}$  (·) is a pair-wise term derived by discontinuous intensity values between neighboring voxels in the image. The unary term is computed from the histograms of the seeds corresponding to the foreground and background. The foreground seeds consist of voxels with high probabilities to belong to the GM from the initial model generated from the atlas-based segmentation since an entire hippocampus belongs to the GM, while the background seeds were defined by the voxels with high probabilities of the WM or the CSF. The seeds of the foreground and background are illustrated in Fig. 1.

#### 2.4. Morphological opening

Morphological operations could be used to remove some imperfections in the segmentation results. In this study, the morphological opening, the erosion followed by dilation with the structuring element, was applied to reduce the false positive results from graph cuts approach. This morphological operation generally makes the contour of an object smooth, breaks narrow isthmuses, or eliminates thin protrusions.

#### 2.5. Validation framework

Several measures were used for the evaluation of three different segmentation results such as original atlas based approach, modified one combined with graph cuts, and its ameliorated version with morphological opening. The similarity index (SI) is derived from a reliability measure known as the kappa coefficient [32]. We computed the kappa coefficient between the manual definition of hippocampus and each segmentation result. This metric measures Download English Version:

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