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Automatic Hippocampal Subfield Segmentation from 3T Multi-modality Images

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Abstract

Hippocampal subfields play important and divergent roles in both memory formation and early diagnosis of many neurological diseases, but automatic subfield segmentation is less explored due to its small size and poor image contrast. In this paper, we propose an automatic learning-based hippocampal subfields segmentation framework using multi-modality 3TMR images, including T1 MRI and resting-state fMRI (rs-fMRI). To do this, we first acquire both 3T and 7T T1 MRIs for each training subject, and then the 7T T1 MRI are linearly registered onto the 3T T1 MRI. Six hippocampal subfields are manually labeled on the aligned 7T T1 MRI, which has the 7T image contrast but sits in the 3T T1 space. Next, corresponding appearance and relationship features from both 3T T1 MRI and rs-fMRI are extracted to train a structured random forest as a multi-label classifier to conduct the segmentation. Finally, the subfield segmentation is further refined iteratively by additional context features and updated relationship features. To our knowledge, this is the first work that addresses the challenging automatic hippocampal subfields segmentation using 3T routine T1 MRI and rs-fMRI. The quantitative comparison between our results and manual ground truth demonstrates the effectiveness of our method. Besides, we also find that (a) multi-modality features significantly improved subfield segmentation performance due to the complementary information among modalities; (b) automatic segmentation results using 3T multimodality images are partially comparable to those on 7T T1 MRI.

1 Introduction

Hippocampal subfields play important and divergent roles in both memory formation and early diagnosis of many neurological diseases. However, due to the small size and poor image contrast, it is less explored. Previously, either manual or automatic hippocampal subfields segmentation depends on ultra-high resolution or 7T/9.4T MR images [1–3], which are not universally available. Hence, it is desirable to develop hippocampal subfields segmentation methods using universal scanners (such as 3T scanner). However, few authors [4] have tried to segment hippocampal subfields using 3T routine T1 MRI and the result is not satisfactory due to low spatial resolution and poor tissue contrast.

Recently, many researches have revealed various connectivity patterns between the hippocampus and other brain regions in fMRI, where different subfields serve for different functions during the brain activities [5,6]. This implies that there might be some distinct

connectivity patterns among different hippocampal subfields, which motivated us to use the rs-fMRI to assist the hippocampal subfields segmentation to achieve better performance with 3T scanners.

In this paper, multi-modality images, including 3T T1 MRI and 3T resting-state fMRI (rs-fMRI), are used together to segment hippocampal subfields in a learning based strategy. In order to get the hippocampal subfields for learning on 3T T1 MRI, both 7T T1 and 3T T1 MRI for each training subject are acquired and the 7T T1 MRI is linearly registered (using Flirt [7]) onto the 3T T1 MRI of the same subject. Six hippocampal subfields (the subiculum (Sub), CA1, CA2, CA3, CA4, and the dentate gyrus (DG), see Fig. 1 (a)) are manually labeled on the aligned 7T T1 MRI, which has the 7T contrast but sits in 3T space. In the next step, corresponding appearance and relationship features from both 3T T1 MRI and 3T rs-fMRI are extracted to train a structured random forest as a multi-label classifier to conduct the segmentation. Finally, the subfields segmentation result is further refined iteratively by additional context features and updated relationship features. To our knowledge, this is the first work that addresses the challenging automatic hippocampal subfields segmentation using 3T routine T1 MRI and rs-fMRI. The quantitative comparison between our results and manual labels demonstrates that the proposed method is quite effective. In addition, we also get two promising conclusions, (a) multimodality features provide complementary information and significantly improve subfields segmentation performance compared to the use of a single modality, and (b) through the proposed method, a comparable segmentation performance is achieved with 3T multi-modality MRI comparing to that using 7T T1 MRI.

2 Motivation and Main Framework

The main challenge of subfields segmentation on 3T routine T1 MRI is the ambiguous subfield boundary caused by low contrast and resolution, as shown in Fig. 1(a-2). To compensate such ambiguity, the relationship features from rs-fMRI are adopted to assist the appearance features from T1 MRI for hippocampal subfields segmentation. Figure 1(b-1) gives an illustration, where patch 1 (belonging to CA2) and patch 2 (belonging to DG) are quite similar in the T1 MRI. It's hard to distinguish them if only using appearance features from T1 MRI. However, if the relationship features (e.g., functional connectivity pattern $\{c_1, \dots, c_{36}\}$) between each patch and the reference regions are obtained from the rs-fMRI (here, 36 is the number of reference regions in our study), then we can potentially distinguish these appearance-similar patches through the differences of their relationship features, as shown in Fig. 1(b-2).

The main workflow of our method is shown in Fig. 2. For a training subject, its appearance features from T1 MRI and relationship features from rs-fMRI are used to train a structured random forest [8] as a multi-label classifier to conduct the segmentation, and then an auto-context model [9] is adopted to refine the classifier iteratively. In the next iteration, the additional context features and the updated relationship features are firstly calculated based on current segmentation probability maps, and then both of them as well as the appearance features are combined to train a new classifier. This procedure will be repeated iteratively to refine the classifier. When a testing subject comes, similarly, the classifier at iteration 0 uses the appearance features and relationship features to generate the segmentation probability

maps; then, the context features and the updated relationship features can be obtained for the iteration **1**. This procedure is also done iteratively until reaching the maximum iteration, where the final segmentation probability maps are used to generate the final segmentation.

In our framework, the appearance features are the 3D Haar features [10] and gradient based texture features [11], which are calculated from the 3T T1 MRI and will not be updated in the whole procedure; the context features are also the 3D Haar features but they are calculated from the segmentation probability maps. The key part is the calculation and updating of the relationship features, which is explained in detail in the following section.

3 Relationship Feature Calculation and Updating

In the preprocessing, the rs-fMRI is linearly registered onto the T1 MRI space [7] for extracting corresponding appearance and relationship features. After that, *first*, the reference regions are constructed, and the connectivity pattern is obtained through the Pearson correlation of fMRI signals between the local patch and each reference region; *second*, this connectivity pattern is enhanced and explored to formulate the final relationship features.

Reference Region Construction and Connectivity Pattern Computation

Since rs-fMRI is from the BOLD signal, a rational assumption is that the BOLD signals are highly correlated inside each subfield, but less correlated across different subfields. So ideally we can choose each subfield as the reference when calculating the connectivity pattern. This is easy for the training images, but is infeasible for testing images since subfields are not segmented yet.

To address this problem, we use a multi-atlas based segmentation [12] to do a rough segmentation, and then obtain the segmentation probability map (See Fig. 3) for each subfield, denoted as $P_{[t]}^{\text{Sub}}, P_{[t]}^{\text{CA1}}, P_{[t]}^{\text{CA2}}, P_{[t]}^{\text{CA3}}, P_{[t]}^{\text{CA4}}$ and $P_{[t]}^{\text{DG}}$, where t denotes iteration in our framework. Note, when $t = 0$, the probability maps are the roughly segmented results by [12]; when $t = 1$, they are the segmentation results by the classifier in each iteration.

By applying a threshold to the probability map, the segmentation of each subfield can be obtained (see Fig. 3). However, it's not appropriate to directly use subfield region as the reference region, because averaging the BOLD signals in the whole subfield might be over-smoothing. To address this issue, we further divide each subfield region into 6 subregions. The advantages of the subdivision include: (a) each subregion is smaller than the whole subfield, which reduces the negative impact caused by over-smoothing; (b) since the segmented subfield might contain mis-segmented voxels from the neighboring subfields, the BOLD signals from divided subregions of this subfield might be more accurate. Also, since the classifier in this paper is structured random forest, it will automatically select the most discriminative features among all subregions to guide the classification.

To make the division of each subfield consistent across different subjects, the division is firstly carried out on one atlas image (or training image), and then the centroid of each subregion is obtained. For a new image, the atlas image is first non-rigidly registered onto it, which provides a deformation field that brings the centroid of each subregion to the new

image. Finally, the subfield can be divided by assigning the label of each voxel with that of the closest centroid.

We use these subregions as the reference regions, and denote the average BOLD signal in each reference region as $\mathbf{b}_k^R$, $k = 1, \dots, 36$, where 36 is the number of reference regions since each of 6 subfields is divided into 6 subregions.

For any voxel i , denoting its mean BOLD signal in the local patch as $\mathbf{b}(i)$, its connectivity to the k -th reference region $c_k(i)$, $k = 1, \dots, 36$, is the Pearson correlation coefficient between $\mathbf{b}(i)$ and $\mathbf{b}_k^R$. Then, for any voxel i , its connectivity pattern to all reference regions is $\mathbf{c}(i) = \{c_k(i), k = 1, \dots, 36\}$, where $\{c_k(i), 1 \leq k \leq 6\}$ is connectivity pattern from subfield ‘Sub’, and $\{c_k(i), 7 \leq k \leq 12\}$ is the connectivity pattern from subfield ‘CA1’, and etc.

Connectivity Pattern to Relationship Features

For two voxels i and j , i.e., i belonging to CA1 and j belonging to CA2, their corresponding connectivity patterns are $\mathbf{c}(i)$ and $\mathbf{c}(j)$. Because each subfield is relatively small, the difference between $\mathbf{c}(i)$ and $\mathbf{c}(j)$ might be subtle, which is less beneficial for classification. Thus, we employ the segmentation probability maps to amplify the difference.

For any voxel i , the probability map values $P_{[t]}^{\mathcal{S}}(i)$ indicate its probabilities belonging to subfield $\mathcal{S}$, where $\mathcal{S} \in \{\text{Sub}, \text{CA1}, \text{CA2}, \text{CA3}, \text{CA4}, \text{DG}\}$. They can be used to weight the connectivity pattern to obtain the weighted connectivity pattern, i.e., $\mathbf{r}(i) = \{r_k(i) | k = 1, \dots, 36\}$, where $r_k(i) = P_{[t]}^{\mathcal{S}}(i) * c_k(i)$. For $1 \leq k \leq 6$, $P_{[t]}^{\mathcal{S}}$ is $P_{[t]}^{\text{Sub}}$; For $7 \leq k \leq 12$, $P_{[t]}^{\mathcal{S}}$ is $P_{[t]}^{\text{CA1}}$, and etc. Through the above formula, the connectivity pattern is weighted according to current predicted segmentation probability maps and thus become more discriminative. For each voxel, a 36 dimensional weighted connectivity pattern can be obtained. So, for the whole image, 36 weighted connectivity maps can be obtained. Then, the 3D Haar features can be extracted from those weighted connectivity maps to explore more patterns. Finally these Haar features form our relationship features.

In our study, 100 Haar features are extracted for each voxel from its local patch in each of the 36 weighted connectivity maps. Thus, totally $36 * 100 = 3600$ relationship features are used for each voxel.

Updating the Relationship Features

At each iteration of the refinement, the segmentation probability maps are updated according to the prediction of the current classifier, which will be used to update the reference regions. Then, the new relationship features can be updated according to the new reference regions and new segmentation probability maps. In such a way, the relationship features can be updated at each iteration.

4 Experiments

Materials

Each subject has 7T T1 MRI, 3T T1 MRI and 3T rs-fMRI data. The 3T scanner (Siemens Trio scanner) of T1 parameters were TR = 1900 ms, TE = 2.16 ms, TI = 900ms and with isotropic 1 mm resolution. Rs-fMRI scans were performed using a gradient-echo EPI sequence and the parameters were as follows: TR = 2000 ms, TE = 32 ms, FA = 80, matrix = 6464, resolution = $3.75 \times 3.75 \times 4 \text{ mm}^3$. A total of 150 volumes were obtained by 5 mins. The 7T scanner (Siemens Magnetom) of T1 parameters were TR = 6000 ms, TE = 2.95 ms, TI = 800/2700 ms and with isotropic 0.65mm resolution. 6 hippocampal subfields for 8 subjects (with ages of 30 ± 8 years) are manually labeled. Then, the leave-one-out strategy is adopted to evaluate the performance of the proposed method.

Segmentation Performance Analysis

A typical hippocampal subfield segmentation result is demonstrated in Fig. 4 by overlapping our result on 3T MRI. By comparing with manual segmentation results, it can be seen that our method can effectively segment hippocampal subfields.

The quantitative analysis is reported in Table 1. Each entry shows mean $\pm$ standard deviation of Dice ratios in a leave-one-out cross validation (only mean value is reported for J. Pipitone's work [4], where they also used 3T structural MRI, but treated CA2 and CA3 (or CA4 and DG) as one subfield). From the table, it can be seen that the segmentation results using combined T1 MRI and rs-fMRI at 3T are consistently better than those using only one single modality. The consistently increased mean value and decreased standard deviation indicate that multi-modality data provides complementary information, which is beneficial for subfield segmentation.

Besides, our result is also compared to the result of using 7T T1 MRI with the same appearance features as the 3T T1 MRI. The comparison result is also reported in Table 1. Comparing the fourth and fifth rows in the table, it can be seen that by using the complementary features from 3T T1 MRI and 3T rs-fMRI, the segmentation results (CA1 – CA4) are comparable to those obtained using 7T T1 MRI. However, for the subiculum (Sub) and dentate gyrus (DG), more discriminative appearance features from 7T T1 MRI seem beneficial, and the results using 3T MRI are inferior. However, in most clinical settings, considering 7T scanners are not available, our approach has the practical advantage.

Segmentation Refinement Evaluation

The segmentation results using different numbers of iterative refinement are reported in Fig. 5 (with the mean Dice ratio). From the figure, it can be seen that the iterative segmentation refinement is quite effective, especially in iteration 1 and 2. The reason is, at each step, the previous segmentation result provides tentative label predictions of the neighboring voxels, which can be used to learn the relationship among neighboring predictions in the random forest. This information refines voxel-wise segmentations that are performed independently. In our case, after iteration 2, the segmentation results become stable. So two iterations are used in this paper.

5 Conclusion

In this paper, we utilize multi-modality images, i.e., 3T T1 MRI and 3T rs-fMRI, to segment hippocampal subfields. This automatic segmentation algorithm uses a structured random forest as the multi-label classifier, followed by iterative segmentation refinement. To the best of our knowledge, this is the first work that investigates hippocampal subfield segmentation using the 3T routine T1 MRI and rs-fMRI. The quantitative comparison between our results and the manually labeled subfields showed that our method is effective. Through these experimental results, we have reached two promising conclusions, (a) multi-modality features can provide complementary information which significantly improves the subfield segmentation compared to the single modality; (b) the segmentation results using 3T scanner are comparable to those obtained using 7T scanner. This shows a clear clinical advantage of our hippocampal subfield segmentation method using 3T multi-modality MRI, considering that the 7T scanner is currently not available in clinical assessment.

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Fig. 1.

(a) Hippocampal subfields demonstration in 7T and 3T MRI, as well as their manual segmentations. (b) Main idea of using relationship features for subfields segmentation.

Fig. 2.
The segmentation refinement procedure via the auto-context model.

Fig. 3.
Demonstration of constructing reference regions from the segmentation probability map of one subfield.

Fig. 4.
Subfield segmentation results demonstration for one subject.

Fig. 5.
Subfield segmentation results (mean Dice ratio) at different iterations.

Table 1

Segmentation performance using different image modalities. Bolded numbers indicate the best performance using 3T MRI scanner.

	Sub	CA1	CA2	CA3	CA4	DG
3T T1	0.63±0.15	0.64±0.17	0.63±0.14	0.65±0.11	0.66±0.15	0.53±0.13
3T rs-fMRI	0.61±0.13	0.65±0.11	0.62±0.07	0.61±0.08	0.64±0.08	0.46±0.15
3T T1 + rs-fMRI	0.68±0.05	0.68±0.10	0.66±0.06	0.67±0.06	0.69±0.05	0.57±0.10
7T T1	0.75±0.04	0.68±0.09	0.68±0.04	0.68±0.06	0.72±0.04	0.65±0.09
J. Pipitone [4]	0.58	0.56	0.41	0.68		