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A fast approach for hippocampal segmentation from T1-MRI for predicting progression in Alzheimer's disease from elderly controls

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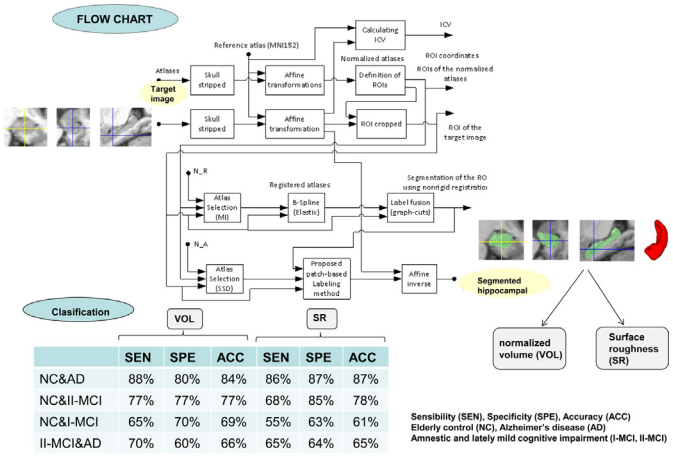
HIGHLIGHTS

- A patch-based labeling method for the hippocampal segmentation is applied.
- Our segmentations show accuracy and robustness using multi-site data.
- Two markers from the hippocampus segmentation are used for predicting progression in AD.
- Validated on predicting AD from elderly controls.
- The source code is available online.

GRAPHICAL ABSTRACT



	SEN	SPE	ACC	SEN	SPE	ACC
NC&AD	88%	80%	84%	86%	87%	87%
NC&II-MCI	77%	77%	77%	68%	85%	78%
NC&I-MCI	65%	70%	69%	55%	63%	61%
II-MCI&AD	70%	60%	66%	65%	64%	65%

Sensibility (SEN), Specificity (SPE), Accuracy (ACC)
Elderly control (NC), Alzheimer's disease (AD)
Amnestic and lately mild cognitive impairment (I-MCI, II-MCI)

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ABSTRACT

Background: We provide and evaluate an open-source software solution for automatically measuring hippocampal volume and hippocampal surface roughness based on T1-weighted MRI, which allows for discriminating between patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) and elderly controls (NC) using only one scan.
New method: This solution is based on a fast multiple-atlas segmentation technique, which combines a patch-based labeling method with an atlas-warping using non-rigid registrations.
Results: The classifications are comparable to the best classifications in a large clinical dataset. For AD vs control, we obtain a high degree of accuracy, approximately 90%. For MCI vs control, we obtain accuracies ranging from 70% to 78%. The average time for the hippocampal segmentation from a T1-MRI is less than 17 min.
Comparison with existing method: In this study, we investigate a combination of our method with annotations using the Harmonized Hippocampal Protocol (HarP). We compare its capabilities with the FreeSurfer method and verify its impact on segmentation and diagnostic group separation capabilities. Our approach is developed and validated using 134 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database with annotations from HarP. Then, this method, tuned with the best parameters, is applied to 162 subjects from a private image database.

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Conclusions: Our approach with HarP annotations has a high level of accuracy for segmentation of the hippocampus and is robust to multi-site data. The bio-markers extracted from our proposed method have discriminative power based on a scalar feature, showing robustness in generalization and avoid overfitting. The computational time in our hippocampal segmentation algorithm has decreased considerably compared to other available analysis.

1. Introduction

The analysis of the hippocampus is a very active field of research because it is one of the first structures where early Alzheimer's disease (AD) pathology is observed (Jack et al., 2004). Patients suffering from the initial stages of AD are mostly clinically classified as amnestic mild cognitive impairment (MCI), but not all patients with amnestic MCI will develop AD (Dubois et al., 2007). It has been shown that measurements of the hippocampus from T1-weighted (T1-W) MRI are useful markers of AD and progression of the clinical decline at a MCI stage (Dubois et al., 2007; Frisoni et al., 2010). A challenge of the neuroimaging is to help in the diagnosis of early AD, particularly in amnestic MCI patients or prodromal AD.

Several approaches have been proposed for automatically classifying patients with AD and/or MCI from hippocampal segmentations (Cuingnet et al., 2011). The manual segmentation of the hippocampus is considered the gold standard but is time consuming (Clerx et al., 2013). Several studies have demonstrated that hippocampal volumetry from the manual segmentation can distinguish patients with AD from controls with a high degree of accuracy (80–90%) and that the discrimination between MCI patients and controls is substantially lower (60–74%) (Gerardin et al., 2009). The manual segmentation of the hippocampus requires considerable training and consumes more than 1 h of work. Consequently, many automatic approaches have been proposed for extracting the hippocampal structures from brain MRI (Collins and Pruessner, 2010; Lotjonen et al., 2010; Leung et al., 2010; Coupé et al., 2011; Wang et al., 2013). Among such approaches, atlas-based methods have been demonstrated to outperform other algorithms (Nestor et al., 2013) that rely on manual segmentations. However, the hippocampus is a complex anatomical structure, and different manual segmentation protocols have been proposed. In fact, a review by Konrad et al. (2009) identified 71 hippocampal tracing methods. The absolute volume differences between certain protocols may vary by 30%. The lack of an agreed reference procedure for manual segmentation is a major barrier to the widespread acceptance and use of hippocampal measures for clinical diagnosis. Defined standard operating procedures for hippocampal segmentation are required for its concrete use as an element to extract bio-markers. Furthermore, the disease status of subjects used in the atlas set may affect the results obtained on a different data set. Most studies have atlases based on normal controls (Fischl et al., 2002; van der Lijn et al., 2008; Chupin et al., 2009; Coupé et al., 2011; Wang et al., 2013). Atlases should be customized for the pathological studies. An international effort to harmonize existing protocols has defined the Harmonized Hippocampal Protocol (HarP) (Boccardi et al., 2011; Frisoni et al., 2015). This protocol proved to be very reliable and to provide a hippocampal segmentation estimate that can be considered as a standard measure, enabling the use of the hippocampal measures as proper bio-markers for AD and MCI.

After obtaining the segmentation of the hippocampus, several bio-markers have been proposed. Generally, the analysis of the volume and/or shape of this anatomical structure is used. The hippocampal volume using MRI is the main criterion for allowing a diagnosis of AD (Dubois et al., 2007; Chupin et al., 2009; Leung et al., 2010; Cuingnet et al., 2011). This bio-marker enables a separation between AD and normal controls (NC) with an accuracy of approximately 72–74% over the entire Alzheimer's Disease Neuroimaging Initiative (ADNI) database (Cuingnet et al., 2011). This limited capability to classify AD patients using only the volume may be due to both a simplification of the atrophy patterns to a global measure and discrepancies caused by the manual protocols. Not only is there interest regarding the hippocampal volume in a unique sample but it has also been observed in measuring volume changes over time (Leung et al., 2010). In Wolz et al. (2010), the authors reported a correct classification rate of 82% for NC versus AD on 568 images of the ADNI dataset. However, this type of approach requires several scans for a given patient. Additionally, volumetric analyses do not provide information about the precise locations of morphological changes that characterize the appearance and progression of AD.

Recently, several methods for the regional hippocampal shape analysis have been proposed (Csernansky et al., 2005; Gerardin et al., 2009; Gutman et al., 2009) for capturing detailed hippocampal structural modifications to obtain a more accurate classification. In the comparison of approaches with the same images (Gerardin et al., 2009), methods based on shape analysis (Gerardin et al., 2009) yield slightly better classification than volumetric approaches. Furthermore, shape analysis approaches allow for the identification of regions in the hippocampus between NC and disease groups, which contributes to the prediction of the conversion from MCI to AD (Csernansky et al., 2005; Gutman et al., 2009; Kim et al., 2015).

An emerging method is to segment subfields of the hippocampus (Van Leemput et al., 2009; Iglesias et al., 2015; Yushkevich et al., 2010, 2015). This approach appears promising because it is potentially able to detect more detailed atrophic patterns. However, ultra-high resolution MRI is required, which is not yet the standard in clinical practice and thus currently limits the practical applicability of this approach.

Therefore, the development of new methods capable of estimating subtle anatomical modifications of the hippocampus appears to be critical for obtaining a better classification rate.

In this study, we use an atlas-based segmentation with annotations from the HarP. We compare our approach with the FreeSurfer method (Fischl et al., 2002) and verify its impact on segmentation and diagnostic group separation capabilities. Two bio-markers, namely, the normalized hippocampal volume and the hippocampal surface roughness, are used for evaluating the segmentation algorithms using their capabilities to detect structural changes caused by AD. For this purpose, we used the ADNI database and a particular image database.

The contribution of this paper is a flow-chart for the automated hippocampal segmentation based on multi-atlas segmentation with the HarP. The approach relies on local contexts by patches representation in both intensity and labeling, allowing constraints on the shape prior, which is essential in the acquisition of the hippocampus using T1-MRI due to the low contrast in intensity. Our segmentation results, guided by the HarP, make the bio-markers used for detecting AD more robust compared to other approaches.

2. Materials

In this study, two database were used to validate the proposed approach and compare it to FreeSurfer: (i) a subset of the ADNI