NeuroImage: Clinical 12 (2016) 825–831

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Reliability of measuring regional callosal atrophy in neurodegenerative diseases

Jeroen Van Schependom, MSc Eng, PhD[a,c,*], Saurabh Jain, MSc Eng[b], Melissa Cambron, MD[a], Anne-Marie Vanbinst, MD[c], Johan De Mey, MD, PhD[c], Dirk Smeets, MSc Eng, PhD[b], Guy Nagels, MD, PhD, MSc Eng[a,d,e]

[a] Center for Neurosciences, UZ Brussel, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium
[b] Icometrix NV, Kolonel Begaultlaan 1B, 3012 Leuven, Belgium
[c] Radiology, UZ Brussel, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium
[d] Faculté de Psychologie et des Sciences de l'Education, Place du Parc 20, 7000 Mons, Belgium
[e] National MS Center Melsbroek, Vanheylenstraat 16, 1820 Melsbroek, Belgium

ARTICLE INFO

Article history:
Received 18 August 2016
Accepted 13 October 2016
Available online 15 October 2016

Keywords:
Corpus callosum segmentation
Biomarker
Repeatability
Reproducibility
Multiple sclerosis
Alzheimer's disease
Corpus callosum thickness profile

ABSTRACT

The Corpus Callosum (CC) is an important structure connecting the two brain hemispheres. As several neurodegenerative diseases are known to alter its shape, it is an interesting structure to assess as biomarker. Yet, currently, the CC-segmentation is often performed manually and is consequently an error prone and time-demanding procedure. In this paper, we present an accurate and automated method for corpus callosum segmentation based on T1-weighted MRI images.

After the initial construction of a CC atlas based on healthy controls, a new image is subjected to a mid-sagittal plane (MSP) detection algorithm and a 3D affine registration in order to initialise the CC within the extracted MSP. Next, an active shape model is run to extract the CC. We calculated the reliability of most popular CC features (area, circularity, corpus callosum index and thickness profile) in healthy controls, Alzheimer's Disease patients and Multiple Sclerosis patients. Importantly, we also provide inter-scanner reliability estimates.

We obtained an intra-class correlation coefficient (ICC) of over 0.95 for most features and most datasets. The inter-scanner reliability assessed on the MS patients was remarkably well and ranged from 0.77 to 0.97.

In summary, we have constructed an algorithm that reliably detects the CC in 3D T1 images in a fully automated way in healthy controls and different neurodegenerative diseases. Although the CC area and the circularity are the most reliable features (ICC > 0.97); the reliability of the thickness profile (ICC > 0.90; excluding the tip) is sufficient to warrant its inclusion in future clinical studies.

1. Introduction

The Corpus Callosum (CC) is the most important fibre bundle relaying information between homologous cortical areas. The mid-sagittal CC Area (CCA) is considered an indicator of the number of small-diameter fibres involved in higher order cognitive functions [Aboitiz, 1992] and a larger CCA has been hypothesized to reflect improved interhemispheric communication [Luders et al., 2007]. Consequently, several studies have found a positive correlation between CCA and intelligence scores [Luders et al., 2007; Luders et al., 2009; Park et al., 2008]. These findings were further corroborated by a post-mortem study of Albert Einstein's brain [Men et al., 2014], in which a significant increase in width – especially in the splenium – was found when compared to healthy controls. In contrast to these findings, some studies have also shown a negative correlation between CCA and intelligence [Ganjavi et al., 2011].

Alterations to the CC morphometry have been shown to be present in different (neurodegenerative) pathologies. An increased CC Area (CCA) was observed in children affected with Autism Spectrum Disorder [Wolff et al., 2015] and smaller CCAs were found in Schizophrenia patients [Bachmann et al., 2003; Rotarska-Jagiela et al., 2008]. Regional CC atrophy was observed in patients affected by Alzheimer's disease [Frederiksen et al., 2011; Hallam et al., 2008; Di Paola et al., 2010], in patients with Huntington's dementia [Di Paola et al., 2012; Rosas et al., 2010], in a sample of patients with mesial temporal lobe epilepsy [Schneider et al., 2014] and in patients with bipolar disorder [Sarrazi et al., 2015].

In Multiple Sclerosis, a neuro-inflammatory disease with a neurodegenerative component, correlations have been established between the Corpus Callosum Area (CCA) and the Expanded Disability Status Scale

* Corresponding author.
E-mail addresses: Jeroen.Van.Schependom@vub.ac.be (J. Van Schependom), Saurabh.jain@icometrix.com (S. Jain), Melissa.cambron@uzbrussel.be (M. Cambron), AnneMarie.Vanbinst@uzbrussel.be (A.-M. Vanbinst), Johan.Demey@uzbrussel.be (J. De Mey), Dirk.Smeets@icometrix.com (D. Smeets), Guy.Nagels@vub.ac.be (G. Nagels).

http://dx.doi.org/10.1016/j.nicl.2016.10.012

(assessing physical handicap) and the Symbol Digit Modalities Test (assessing information processing speed) [Granberg et al., 2015]. In addition - in the same study - the CCA outperformed whole-brain, lesion, white and grey matter volume in discriminating between healthy controls (HC) and MS patients. Finally, CC atrophy during the first year of treatment was found to be the best predictor (comparing to T1 and T2 lesion volumes and, brain parenchymal fraction and atrophy) of disability and its increase in a large and long-running (9 years) follow-up study [Vaneckova et al., 2012].

Due to the increasing interest in analysing the regional influence of different (neurodegenerative) pathologies on the CC, recent research has included the corpus callosum thickness profile as an important feature [Walterfang et al., 2009]; e.g. a recent study found that the regional thickness could predict the conversion from mild cognitive impairment to Alzheimer's disease [Lee et al., 2016].

Although most thickness profile generation methods rely on the orthogonal projection outward from a midline [Adamson et al., 2011], overlap between adjacent streamlines may lead to biased results inflating the thickness in more curved CC. As presented in [Adamson et al., 2014], the use of a continuous thickness calculation based on an artificial Laplacian field bypasses this limitation. Furthermore, it provides a biologically plausible model as the resulting thickness profiles are similar to the underlying organisation of the connections from the CC [Adamson et al., 2011; Hofer and Frahm, 2006] and omits the need of subdividing the CC using different partition schemes [Luders et al., 2007] (e.g. the Witelson partition [Witelson, 1989]).

Several strategies have been developed to segment the mid-sagittal plane (MSP) CC from T1-weighted magnetic resonance images. These strategies can be roughly divided into three categories [Herron et al., 2012]: a first set of methods is based on whole-brain registration to one (or multiple) common space(s) [Adamson et al., 2014; Ardekani et al., 2005; Chaim et al., 2007; Wang et al., 2009]. While the main advantage of these methods is that the CC does not need to be delineated in individual images (but only on the template), these methods lack the flexibility to capture the large inter individual differences in CC shape and require manual intervention in up to 20% of the cases [Adamson et al., 2011; Ardekani et al., 2014; Wang et al., 2009]. Furthermore, the robustness of more advanced deformation-based techniques is not clear [Herron et al., 2012], especially with respect to neurodegenerative diseases.

A second strategy relies on pre-defined rules. However, these methods seem to be vulnerable to segmentation errors (e.g. the fornix and pericallosal arteries [Herron et al., 2012]) and may not be suitable to segment the CC in various neurodegenerative diseases.

As we expected that neither deformation-based techniques, neither rule-based techniques could be reliably applied to the segmentation of the CC in patients affected by neurodegenerative diseases, we developed a method that belongs to the boundary based methods, that rely on a set of manually delineated CCs that are fed into an active shape model. As such, the variations observed in the training set limit the shape variations allowed in test-images. While the main disadvantage of these boundary-based methods seems to be the necessity to develop specific training sets for every (neurodegenerative) population, we aim at assessing to what extent this disadvantage is justified.

In this paper, we provide accuracy (comparison to manual segmentations), repeatability (subject stayed within the scanner) and reproducibility (patient was repositioned for a new scan) estimates for the most commonly used CC features (area, circularity, corpus callosum index [Figueira et al., 2007]) and the thickness profile calculated using Laplace's equation, both in healthy controls and in two neurodegenerative populations. Our aim is to provide an insight into the reliability of the different CC features and to assess whether the thickness profile – which can be easily calculated and provides more detailed information than the commonly used CC features – can be as reliably extracted as more robust features like the CC area.

2. Methods

2.1. Datasets

2.1.1. Dataset 1. Healthy controls and Alzheimer's patients from the OASIS database

The OASIS database consists of 416 subjects aged between 18 and 96 years old. For each subject, 3 or 4 individual T1-weighted MRI scans obtained in single-scan sessions were included. The scans were acquired on a 1.5-T Vision scanner (Siemens). All subjects are right-handed and female. Out of the 416 scanned subjects, 100 have been clinically diagnosed with very mild to mild Alzheimer's disease (AD) according to the Clinical Dementia Rating [Marcus et al., 2007; Morris et al., 2001]. Additionally, a reliability dataset of 20 non-demented subjects imaged on a subsequent visit within 90 days of their initial session was provided (oasis-brains.org). For more information, cf. [Marcus et al., 2007].

From the OASIS database we applied the algorithm to the 216 healthy controls that were not used for training and 100 patients affected by very mild to mild Alzheimer's Disease. For these patients, 3 to 4 scans are available. Rather than averaging the different scans to increase the signal-to-noise ratio, we processed the different scans independently. This allowed us to assess the repeatability of our algorithm. The 216 healthy controls are referred to as “OASIS_HC”, the 100 AD patients as “OASIS_AD”.

Furthermore, 20 non-demented subjects had been scanned twice within 90 days. These patients are denoted as “OASIS_HC_TRT”.

2.1.2. Dataset 2. Multiple sclerosis patients

Ten MS patients participated in a study at University Hospital UZ Brussel, Brussels, Belgium. The study was approved by the local ethics committee and all patients signed informed consent forms. MR imaging was performed for each patient twice on 3 3T whole body scanners from 3 different manufacturers (GE Medical Systems Discovery MR750 MW, SIEMENS Skyra, Philips Medical Systems Achieva). The patient was re-positioned between the first and the second scan. The GE scanner protocol contained, among others, a 3D T1-weighted FSPGR sequence (TR 7.32 ms, TE: 3.144 ms, FA 12°, 220×220 mm^2 FOV, 328 sagittal slices, $0.4297 \times 0.4297 \times 0.5$ mm^3 voxel resolution). The SIEMENS scanner protocol contained a 3D-T1-weighted MPRAGE sequence (TR: 2300 ms, TE: 2.29 ms, FA 8°, 240×240 mm^2 FOV, 176 sagittal slices, $0.9375 \times 0.935 \times 0.94$ mm^3 voxel resolution) and the PHILIPS scanner protocol contained a 3D T1-weighted FPSR sequence (TR 4.936 ms, FA 8°, 230×230 mm^2 FOV, 310 sagittal slices, $0.5324 \times 0.5324 \times 0.5$ mm^3 voxel resolution).

2.2. Construction of a CC training atlas

The training set consisted of 100 images from the OASIS dataset for which the corpora callosa were manually delineated on their respective Mid Sagittal Planes (MSPs). Next, a minimum description length algorithm was applied in order to solve the point correspondence problem (i.e. ensuring maximal correspondence between the n'th point on the CC boundary among the different images) [Thodberg, 2003]. The subjects used in this step are excluded from the analysis in which repeatability of the different CC features is assessed.

As a CC shape consisted of >3000 edge points, that – in theory – could all move independently, a principal component analysis on these shapes was performed to retain 99% of the observed variance in the constructed atlas (corresponding to 16 principal components). The shape variations along the first 3 principal components are depicted in Fig. S1. Once a new image is entered in the pipeline, these 16 principal components will ensure a regularisation on the possible shapes and will ensure that the fornix is not included in the segmentation.

This way, we have constructed a training atlas (cf. Fig. 1) containing the average shape and the principal components of the shape variations