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Callosal circularity as an early marker for Alzheimer's disease

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ABSTRACT

Background: Although brain atrophy is considered to be a downstream marker of Alzheimer's disease (AD), subtle changes may allow to identify healthy subjects at risk of developing AD. As the ability to select at-risk persons is considered to be important to assess the efficacy of drugs and as MRI is a widely available imaging technique we have recently developed a reliable segmentation algorithm for the corpus callosum (CC). Callosal atrophy within AD has been hypothesized to reflect both myelin breakdown and Wallerian degeneration.

Methods: We applied our fully automated segmentation and feature extraction algorithm to two datasets: the OASIS database consisting of 316 healthy controls (HC) and 100 patients affected by either mild cognitive impairment (MCI) or Alzheimer's disease dementia (ADD) and a second database that was collected at the Memory Clinic of Hospital Network Antwerp and consists of 181 subjects, including healthy controls, subjects with subjective cognitive decline (SCD), MCI, and ADD. All subjects underwent (among others) neuropsychological testing including the Mini-Mental State Examination (MMSE). The extracted features were the callosal area (CCA), the circularity (CIR), the corpus callosum index (CCI) and the thickness profile.

Results: CIR and CCI differed significantly between most groups. Furthermore, CIR allowed us to discriminate between SCD and HC with an accuracy of 77%. The more detailed callosal thickness profile provided little added value towards the discrimination of the different AD stages. The largest effect of normal ageing on callosal thickness was found in the frontal callosal midbody.

Conclusions: To the best of our knowledge, this is the first study investigating changes in corpus callosum morphometry in normal ageing and AD by exploring both summarizing features (CCA, CIR and CCI) and the complete CC thickness profile in two independent cohorts using a completely automated algorithm. We showed that callosal circularity allows to discriminate between an important subgroup of the early AD spectrum (SCD) and age and sex matched healthy controls.

1. Introduction

Volumetric magnetic resonance imaging (MRI) is of increasing importance in the follow-up of patients with mild cognitive impairment (MCI) or Alzheimer's disease (AD) (Filippi et al., 2012), with most attention being devoted to atrophy of the medial temporal lobe (MTL), hippocampus or entorhinal cortex. Although atrophy in these latter structures is considered to be a downstream topographical biomarker of AD with a limited value for early (preclinical) AD diagnosis (Dubois et al., 2014), it may provide a tool to follow up AD patients (Frisoni et al., 2010).

Whereas most studies report a high intra-class correlation coefficient (ICC) between automated and manual segmentation of the hippocampi, e.g. (Plassard et al., 2017; Zandifar et al., 2017), others report a low ICC (Akudjedu et al., 2018). Yet, segmentation of the entorhinal cortex often requires manual segmentation due to its inter subject variability, relatively small size and low contrast with surrounding structures. Although being time consuming, manual segmentation approaches have been widely used and are even a standard approach by experts in neuroanatomy (Boccardi et al., 2011). However, the number of large-scale studies is limited. Although semi-automated techniques are less time consuming, a priori information such as user-defined landmarks are needed, which also limits their usefulness for large clinical studies (Kennedy et al., 2010). To save time and costs,

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automated methods have been proposed, which can be used in larger study populations and can be reproduced more easily.

Sensitive and reliable markers are needed to monitor disease progression or therapy response. As the whole-brain atrophy rate has been estimated at 1.4–2.2% in AD as compared to 0.7% in age-matched controls (Frisoni et al., 2010), it has been suggested as a marker to follow up AD patients. Yet, by assessing whole-brain atrophy, a lot of specificity is lost.

Therefore, an alternative MRI marker could be atrophy of the corpus callosum (CC) (Di Paola et al., 2010a, 2010b; Frederiksen et al., 2011; Hampel et al., 2002, 1998; Lyoo et al., 1997; Ortiz Alonso et al., 2000; Teipel et al., 2002, 1999, 1998; Thompson et al., 1998; Van Schependom et al., 2017; Wang et al., 2006; Yamauchi et al., 2000; Zhu et al., 2012). While callosal atrophy has been shown in AD and has been hypothesized to originate from myelin breakdown in the anterior CC regions and from Wallerian degeneration in posterior regions (Di Paola et al., 2010a, 2010b), both the affected CC region and the timing at which callosal atrophy can be observed are under debate. While some studies found differences in the posterior regions in early onset AD (Yamauchi et al., 2000), MCI patients (Wang et al., 2006), and mild AD dementia (ADD) patients (Frederiksen et al., 2011; Hampel et al., 2002; Lyoo et al., 1997; Wang and Su, 2006), others observed differences in the anterior regions in MCI (Zhu et al., 2012) and moderate ADD (Ortiz Alonso et al., 2000). Only one study assessed severe ADD patients and found differences in both anterior and posterior regions (Di Paola et al., 2010a, 2010b).

Apart from the CC area, one study found differences in circularity (ratio of the area to the perimeter) already in MCI patients (Ardekani et al., 2014) suggesting that morphological CC features may be more sensitive to disease specific changes than plain area.

As the CC can be automatically and reliably extracted from 3D T1 MR images (even in neurodegenerative diseases (Van Schependom et al., 2016)) and likely provides more detailed information than whole-brain atrophy, we aim at assessing its value in AD in two independent cohorts. The first cohort is the OASIS database, which contains a large number of subjects (100 ADD patients, 316 healthy controls). The second one is a monocentric cohort, collected at UAntwerp, covering the entire AD continuum. As a reference, we will also assess the effect of normal ageing in both cohorts.

Next to assessing overall features (area - CCA, circularity - CIR and CC index - CCI) or applying an artificial division of the CC into different sub regions, we will also calculate a thickness profile of equidistantly sampled streamlines along the CC midline. This method ensures non-crossing streamlines orthogonal to the boundaries and provides a ‘natural’ division of the CC while bypassing inherent problems that arise when trying to divide the CC in different regional areas (Adamson et al., 2011; Luders et al., 2007; Tomaiuolo et al., 2007).

2. Materials and methods

2.1. Study population 1: OASIS cohort

The OASIS database consists of 416 subjects aged 18–96. 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 were right-handed.

Control subjects under the age of 60 were questioned about their medical histories and use of psychoactive drugs. For subjects older than 60 years, a global Clinical Dementia Rating (CDR, (Morris, 1993)) score (based on a collateral source and subject interview) was recorded. Furthermore, it is outlined by Markus et al. that *subjects with alternative primary causes of dementia* (e.g. *vascular dementia*, *primary progressive aphasia*), *active neurological or psychiatric illness* (e.g. *major depression*), *serious head injury*, *history of clinically meaningful stroke*, *and use of psychoactive drugs were excluded*, *together with subjects with gross anatomical abnormalities evident in their MR images* (e.g. *large lesions*, *tumors*) (Marcus et al., 2007).

Out of the 416 available subjects, 70 subjects had been diagnosed with MCI (“very mild AD”, according to the Clinical Dementia Rating (Morris, 1993), CDR = 0.5) while 28 subjects have been diagnosed with mild Alzheimer's Disease Dementia (mADD, CDR = 1) (Morris et al., 2001). Only the first of the 3–4 available MR T1-weighted scans was used for this analysis, although no differences are expected when one would use the other scans thanks to the high inter scan reliability (Van Schependom et al., 2016). For more information on this dataset, cf. (Marcus et al., 2007).

As the CC is suspected to be larger in females than in males (after correcting for intracranial volume) (Ardekani et al., 2013), we matched subgroups from the OASIS database to the clinical populations. Matching was performed on sex and age. Additional data on the subjects included in the OASIS database were sex, age, education, socio-economic status (SES, (Rubin et al., 1998)) and the Mini-Mental State Examination (MMSE) which is a widely used screening instrument for dementia (Folstein et al., 1975; Rubin et al., 1998).

2.2. Study population 2: UAntwerp cohort

The second database was collected at the Memory Clinic of Hospital Network Antwerp and consists of 181 subjects, including healthy controls, subjects with subjective cognitive decline (SCD), MCI, and ADD. All subjects underwent (among others) neuropsychological testing including MMSE.

A clinical diagnosis of dementia due to AD was made by applying the NIA-AA criteria (McKhann et al., 2011). A diagnosis of MCI due to AD was made by the NIA-AA criteria (Albert et al., 2011; Dubois et al., 2014; Jack et al., 2011; Sperling et al., 2011) i.e., (1) cognitive complaint, preferably corroborated by an informant; (2) objective cognitive impairment, quantified as performance of > 1.5 SD below the appropriate mean on the neuropsychological subtests; (3) largely normal general cognitive functioning; (4) essentially intact activities of daily living (basic and instrumental activities of daily living were determined by a clinical interview with the patient and an informant); and (5) not demented. The diagnosis of dementia or MCI due to AD was further corroborated either through AD biomarker analyses ($A\beta_{1-42}$, T-tau, and P-tau_{181}) in cerebrospinal fluid (CSF) according to the IWG-2 criteria (Dubois et al., 2014), based on in-house validated cut-off values (Van Der Mussele et al., 2014), and/or through hippocampal atrophy based on the Scheltens scale (Scheltens et al., 1992).

SCD patients were diagnosed by the Jessen's et al. criteria (Jessen et al., 2014), without an objective cognitive impairment, so all neuropsychological subtests having a z-score above -1.5 SD.

All control subjects underwent at least a cognitive screening test to rule out cognitive impairment. The inclusion criteria for cognitively healthy elderly were: (1) no neurological or psychiatric antecedents; (2) no organic disease involving the central nervous system following extensive clinical examination; and (3) no cognitive complaint or decline.

All subjects provided written informed consent and the study was approved by the ethics committee of University of Antwerp, Antwerp, Belgium.

2.3. Corpus callosum segmentation

The applied algorithm to segment the CC and to extract the different features has been extensively described and validated in both healthy controls and subjects affected with multiple sclerosis or AD (Van Schependom et al., 2016).

In short, our method first automatically extracts the Mid Sagittal Plane (MSP) maximising the symmetry between the two brain hemispheres. This MSP is resampled to voxels of $0.5 \times 0.5\,mm^2$. Next, a 3D affine registration between an MNI template and the patient's MRI allows to translate and rotate an average CC to its initial position within the MSP. In the optimisation step, the (interpolated) pixel intensities