DEFINITION OF AN AUTOMATIC SYSTEM FOR THE MILD COGNITIVE IMPAIRMENT CLASSIFICATION

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Abstract - The present work aims to investigate the existence and applicability of an automatic system able to assess brain atrophy to enable the staging of neurodegenerative diseases such as Alzheimer's. To achieve this, it was necessary to resort to software specifically designed for neuroimaging, conducting multiple analyses.

Keywords - MRI (Magnetic Resonance Imaging), Neurodegenerative Diseases, Free Surfer, Staging, Machine Learning.

I. INTRODUCTION

There are several software tools for processing magnetic resonance imaging (MRI) images, which allow studying the structure and functioning of the brain. Structural imaging focuses on highlighting the brain's structures and anatomy based on the different physical properties of brain tissues. On the other hand, functional imaging aims to investigate cognitive processes by analyzing blood volume or oxygen concentration in the blood, introducing a temporal dimension. The choice of one software over another depends on various factors, with the type of imaging being performed being the primary consideration. Established software packages such as FreeSurfer [1], FSL (FMRIB Software Library), SPM (Statistical parametric mapping) [2], and AFNI (Analysis of Functional Neuroimages) [3] generally encompass both modalities and offer an equivalent set of services. FreeSurfer is undoubtedly one of the most widely used software in the field of brain imaging. It benefits from comprehensive documentation, active developer support, and a user community through mailing lists. It undergoes regular updates aimed at improving its functionality. For these reasons, it has been chosen as the reference application to build an automatic system for Mild Cognitive Impairment Classification.

II. NEUROSCIENTIFIC DATABASES

A better understanding of the functioning of the human brain is key to the prevention and treatment of neurodegenerative diseases such Alzheimer's disease. It is important for doctors and researchers to have access to user-friendly digital platforms capable of collecting and storing significant amounts of three-dimensional brain images and clinical data. There are several projects that aim to achieve this goal, including ADNI (Alzheimer's Disease Neuroimaging Initiative), OASIS (Open Access Series of Imaging Studies) [4], and OpenNeuro [5]. Generally, these projects create multimodal neuroimaging datasets that employ MRI data, clinical data, cognitive data, and biomarkers. For this study, ADNI was chosen, which is a global research group whose objective is to study and find treatments that can slow down or even halt the progression of Alzheimer's disease. Alzheimer's is an irreversible neurodegenerative disease that causes a loss of brain function due to the deterioration of brain tissue. It is the most common cause of dementia among people over 65 years old, and there are currently no known methods of prevention or cure. An essential element of the study is to track the progression of the disease and highlight the differences between normal aging, mild cognitive impairment (MCI), and Alzheimer's-related dementia, using imaging processes and the analysis of clinical, genetic, and biomarker indicators of biological status [6].

The study, which is longitudinal in nature, is divided into four phases: ADNI1, ADNIGO, ADNI2, ADNI3:

- ADNI1 (2004) categorizes participants as: Cognitively Normal (CN), also referred to as Normal (NL), who have normal cognitive levels; MCI (Mild Cognitive Impairment) for individuals with mild cognitive impairment; and AD (Alzheimer's Disease) for those affected by Alzheimer's disease. There are 200 CN, 400 MCI, and 200 AD participants.
- ADNIGO (2009) introduces two new classes: EMCI (early mild cognitive impairment), which represents the stage preceding MCI, and LMCI (late mild cognitive impairment).
- ADNI2 (2011) adds the SMC (Significant Memory Concern) category, which includes individuals who report significant memory problems and fall between CN and MCI.
- ADNI 3 (2016) incorporates brain scans capable of detecting tau protein tangles (tau PET), a key indicator of the disease.

New participants were recruited for each phase of the study, while also continuing to monitor those already enrolled. Figure 1 illustrates the types of examinations performed for each phase and at each visit. A more detailed list of the tests conducted at each visit is available online [7].



Figure 1. Examinations for visit and for phase

III. FREESRUFER

FreeSurfer is an open-source software package for the analysis and visualization of data derived from structural and functional neuroimaging methodologies for cross-sectional studies (analysis at a specific time point) or longitudinal studies (analysis over a period using multiple time points for each patient). We have chosen to work with structural MRI data, for which FreeSurfer provides a highly comprehensive processing pipeline. It includes multiple functionalities such as skull stripping, segmentation of white and gray matter, reconstruction of white and pial surfaces (separating white matter from gray matter and gray matter from cerebrospinal fluid), as well as labeling of regions comprising the cortical surface and subcortical structures. All these processes can be achieved with a single command: recon-all. Moreover, it is possible to perform statistical analysis of morphometric differences within a group of subjects and utilize a processing stream for longitudinal studies. Within the software package, there is also Freeview, a tool for visualizing the volumes and surfaces generated as output by FreeSurfer. As regards the segmentation phase, two approaches were undertaken with two different tools: SAMSEG e ASEG described below. For the processing of magnetic resonance imaging, the development version of the software freesurfer-linux-ubuntu18_x86_64-dev-20220426-a80d23a was used. It was used on a physical machine running Ubuntu 20.04.4 LTS with 32 GB of RAM, 1.79 TB of hard drive space, and 8 cores.

IV. CEREBRAL ATROPHY EVALUATION

Cerebral atrophy involves the permanent reduction of brain tissue and can affect specific areas (such as those involved in language, memory, and learning) or the entire organ, resulting in a decrease in both the numerical and functional aspects of neurons and the connections between them. This condition is characteristic of aging and various neurodegenerative disorders, including Alzheimer's disease. Several methods exist to assess the extent of pathology using imaging diagnostics. Visual rating scales (such as Global Cortical Atrophy and Brain Atrophy and Lesion Index) provide a rapid approach but require extensive expertise from the neuroradiologist, leading to potential differences in interpretation and relatively coarse results. More recently, automated procedures have emerged, enabling operations like tissue segmentation and subsequent volumetric measurement of components such as gray matter, white matter, and cerebrospinal fluid, as well as individual regions, using information from MR image signal intensity. These procedures are user-friendly and provide objective results that are reproducible. From the obtained measurements, changes occurring over time can be monitored and quantified. However, human intervention is still recommended, as manual corrections may be necessary after the segmentation process. The Brain Volume/Cerebrospinal Fluid (BV/CSF) index, which represents the ratio of brain volume to cerebrospinal fluid volume, allows for a measure of global cerebral atrophy. Knowledge of this value enables the determination of disease stage, monitoring of disease progression, and potentially predicting clinical changes [8].

A. Calculation of the BV/CSF index

Two different approaches were used for this purpose: the first uses ASEG for segmentation, which is the default segmentation tool in the recon-all processing pipeline; the second one is based on SAMSEG, which will be discussed later. Both approaches consist of three steps and refer to three different regions as described below.

The first step involves calculating the brain volume, which is obtained as follows: BV = Total GM + Total WM. Here, GM refers to the total volume of gray matter and WM refers to the total volume of white matter. The second step involves calculating the total volume of cerebrospinal fluid (CSF), which is not directly available and needs to be computed. CSF consists of ventricular CSF and sulcal CSF, so the total CSF volume is determined as: Total CSF = Ventricular CSF + Sulcal CSF.
The third step calculates and displays the value of the index obtained from the previous results:

$$\frac{\text{BV}}{\text{CSF}}\,\text{index} = \frac{\text{BV}}{\text{CSF}} = \frac{\text{Total GM} + \text{Total WM}}{\text{Vventricular CSF} + \text{Sulcal CSF}} \quad (1)$$

B. ASEG based calculation index

In the first step, the ASEG algorithm, computes the total volume of gray matter by the metric TotalGray, obtained as the sum of the volumes of all the structures listed in Figure 2 (including the Cerebellum cortex).

The total volume of white matter is computed by the following metrics: CerebralWhiteMatter (which should include the Corpus callosum), Brain-Stem, Left-Cerebellum-White-Matter, and Right-Cerebellum-White-Matter. Regarding the second step, the ventricular contribution is determined by the following metrics: Left-Lateral-Ventricle, Left-Inf-Lat-Vent, Right-Lateral-Ventricle, Right-Inf-Lat-Vent, 3rd-Ventricle, 4th-Ventricle, 5th-Ventricle, Right-choroid-plexus and Left-choroid-plexus. Regarding the sulcal CSF, FreeSurfer, in its reconstruction using the recon-all command, employs the ASEG (Automatic Segmentation) approach, which does not segment this region as it is indistinguishable from bone on a T1-weighted MRI. However, the CSF metric is a measure of the sulcal CSF, albeit with low reliability.

C. SAMSEG based calculation index

The Sequence Adaptive Multimodal SEGmentation (SAMSEG) tool enables the segmentation of brain structures based on one or more MRI scans of the head. It does not require preprocessing of the MRI data and can work with multi-contrast images, independent of the specific scanner or pulse sequence used for acquisition [9]. SAMSEG typically takes approximately ten minutes for processing, while ASEG in recon-all can take several hours . Despite this, SAMSEG is a reliable tool [10]. The number of threads to be used can be specified (by default, one), thereby accelerating the processing of individual tasks. SAMSEG requires the input path of the volume to be processed, which should be in NIfTI or .mgz format (obtained through compression of the proprietary MGH format). MRI data is often organized as collections of DICOM files, so conversion is necessary before providing them as input to the tool.

V. EXPERIMENTAL RESULTS

Multiple experiments were conducted to demonstrate the validity of the BV/CSF index for patient classification. Two tools, namely SAMSEG and ASEG, were used to assess their capabilities. A selection of the conducted experiments is reported below.

A. BV/CSF-index experiment

As a first experiment, we chose to perform the cortical reconstruction process with FreeSurfer on the extreme cases, namely subject 002_S_0685 diagnosed with CN and subject 002_S_0816 diagnosed with AD using theASEG algorithm. The results obtained computing the BV/CSF index, considering the sulcal CSF based on the estimation of total intracranial volume (estimated Total Intracranial Volume - eTIV), are reported in the Table1. In this case, there is a discrepancy between the predictions and the results, because we would have expected a lower value for the AD subject and a higher value for the CN subject.

Subject	002_S_0685	002_S_0816
Total WM	493214.60 mm^3	481901.50 mm^3
Total GM	529134.287120 mm^3	559126.085355 mm^3
BV	1022348.89 mm^3	1041027.59 mm^3
Ventricular CSF	46516.3 mm^3	38831.3 mm^3
Sulcal CSF	437555 mm^3	381197 mm^3
CSF	484071.30 mm^3	420028.30 mm^3
BV/CSF	2.11	2.48

Table 1. Bv/csf index with sulcal csf based on etiv - 002_s_0685 vs 002_s_0816

B. BV/CSF-index in different groups

The second experiment involves three different groups of subjects according to their classification inside the ADNI database: CN, MCI, AD. The test aims to further analyze the BV/CSF index for each group by using the SAMSEG tool over a larger number of images. The results are described in Table 2.

Group CN	002_S_0295	002_S_0413	023_S_0031	033_S_0920	073_S_0089
BV/CSF index	1.94	2.21	2.26	1.89	2.14
Group MCI	010_S_0904	023_S_0078	036_S_1135	051_S_1331	072_S_1211
BV/CSF index	1.99	2.19	2.16	1.59	1.95
Group AD	002_S_0955	002_S_5018	006_S_4546	018_S_5240	041_S_1391
BV/CSF index	1.97	1.82	1.81	2.38	1.73

Table 2. BV/CSF index, multiple subjects per group

For the CN group, the average value is 2.08, for MCI it is 1.97, and for AD it is 1.94. We can observe a slight decrease in the index as the brain atrophy increases.

C. Disease progression experiments

In the third experiment of this group, we focused on the disease progression for a given subject using the SAMSEG tool. It was necessary to identify a patient inside the ADNI database, whose disease progression was of interest so that the diagnosis at baseline was "CN" and the diagnosis at subsequent visits was "Dementia". Using the same methods described in the previous paragraph, the BV/CSF index was calculated. The obtained values are shown in Table 3. The expectations were met as the index showed a lower value in the AD case compared to the CN case.

ImageUID	257270	1075136
Total WM	523723.10 mm^3	515114.40 mm^3
Total GM	757639.71 mm^3	691708.07 mm^3
BV	1281362.81 mm^3	1206822.47 mm^3
Ventricular CSF	47649.33 mm^3	76819.80 mm^3
Sulcal CSF	567626.856430 mm^3	571837.386027 mm^3
CSF	615276.19 mm^3	648657.19 mm^3
BV/CSF	2.08	1.86

Table 3. BV/CSF index CN vs AD

VI. CONCLUSION

This paper focused on neurodegenerative diseases for developing an automatic system for experts to evaluate the cognitive efficiency of patients. This result was achieved by assessing cerebral atrophy using the BV/CSF index with the assistance of the neuroimaging program FreeSurfer.

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