THE LATIN STEREOTACTIC BRAIN MRI ATLAS

VALERIA RIVERA MUNOZ

Escuela de Ingeniería de Sistemas y Computación
Facultad de Ingeniería
Universidad del Valle

September, 2021

THE LATIN STEREOTACTIC BRAIN MRI ATLAS

VALERIA RIVERA MUNOZ

FINAL CAREER PROJECT IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF SYSTEMS ENGINEERING

Advisor:

JOSE BERNAL, PHD

Co-advisors:

MARIA TRUJILLO, PHD

ALEJANDRO HERRERA, MD MSC

Escuela de Ingeniería de Sistemas y Computación
Facultad de Ingeniería
Universidad del Valle

September, 2021

ACKNOWLEDGEMENTS

I would like to thank my advisors and co-advisors for inspiring me, for their invaluable help and their love for teaching. To my classmates and professors, who shared with me, perhaps, the best experience of my life. And specially to my family. To my mom, who has always believed in me more than I believe in myself. To my little brother, who motivates me to be my best version. To my grandmother, who has given me more love than anyone could ever imagine and to my uncle, who has been like a father to me.

ABSTRACT

Brain atlases – also referred to as templates – play a fundamental role in neuroanalysis and neuroscience as they provide a graphical representation of the brain of a certain population. The lower the morphological and volumetric differences between the atlas and the target population, the lower the errors in subsequent analyses. However, numerous procedures rely on the Talairach and Montreal Neurological Institute (MNI) atlases created with scans from French and Canadian subjects, respectively, i.e. they may induce bias in analyses of the Latin or Colombian population. Thus, in this work, we create the first brain atlas of the Latin population to have a reference of normality closer to that of our country. Our methodology for constructing a Latino-American stereotactic brain magnetic resonance imaging (MRI) was as follows. First, we systematically review the literature to determine whether such an atlas already existed and to select relevant techniques and methodologies for building these digital templates. Second, we used the identified approximations to build the atlas. Third, we evaluate the proposed Latino-American atlas by comparing its length, width, height, AC-PC length, and volume to other atlases available in the literature; and assessing the level of deformation needed to register our atlas and already available ones to scans from Latino-American people. Our results over the Latino-American brain atlas against ICBM452 indicated positive aspects when dealing with a new volume from Latino-American population. It requires less global deformation and there is more similarity in size at global and structural levels with our template relative to others. Indeed, these observations indicate that the closer the atlas to the study population, the reduced the bias in subsequent analyses. This, in general terms, would indicate that if there were a study of the Colombian population that required a brain MRI atlas, that atlas should be created with images of the same population in order to obtain a better result.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1 INTRODUCTION

1.1 GENERAL DESCRIPTION

This final career project addresses the creation of a magnetic resonance brain atlas of Latin population. It focuses on the selection of relevant and appropriate computer vision tools and techniques required for each of the stages involved in atlas construction, such as skull stripping, intensity standardisation and image registration. We evaluate our atlas through a quantitative assessment, based on the comparative analysis between the local atlas and other commonly used atlases, respect to an established set of criteria.

1.2 MOTIVATION

Brain atlases provide a graphical representation of the average brain structure of a certain population, as depicted in Fig. 1. These templates have played an important role in neuroanalysis and pre-surgery planning since 1967, when the first clinically relevant atlas became available [14]. Among its many applications, a brain atlas enables teaching neuroanatomy [26]; surgery planning [26]; segmenting and measuring brain structures [18]; comparing and combining scans from multiple subjects acquired using multiple imaging modalities [39]; and detecting structural changes due to ageing, demographics, sex, genotype or disease [15]. The construction methodology as well as the characteristics of the population considered to devise these atlases determines both their visual quality and relevance. The closer the atlas to the study population, the reduced the bias in subsequent analyses [15].

1.3 HYPOTHESIS

Atlases are fundamental reference objects in geography, but also in neuroscience [33]. However, unlike in geography, humans exhibits distinct brain characteristics that prevent singularity [33]. Given that none of the available atlases has been devised using scans from the latin population, they may not reflect the latin brain phenotype. We hypothesise the average Latin brain has structural, morphological and volumetric characteristics that are different from those from other regions of the world.

Figure 1: Brain atlases developed over the years. The result of varying the number of people involved in the study can be seen by comparing the average305 with the collin27, the two atlases on the left. The first one was performed with 305 MRIs from different people, while the colin 27 was performed with MRIs from the same person, there is a considerable difference between them despite using the same type of registration to create both atlases. The impact of the type of registration used can be noticed in the two atlases on the right. The ICBM152 was made with a rigid registration, while the NL ICBM 152 was made with a non-rigid registration. Both of them with the same amount of MRIs. However, even if visually, they differ in definition of brain structures, While a sharp image would be preferred, sharpness is not a synonym for relevance.

1.4 PROJECT JUSTIFICATION

This project is part of a macro-project called "Biomarkers *in silico*" developed by a multidisciplinary group from the Imbanaco Medical Center and students from the Universidad del Valle. The current work is oriented to the creation of a Latin magnetic resonance atlas. It corresponds to the analysis and coregistration of images prior to stereoelectroencephalography and of pre and post surgical images. The Fig. 2 shows the structure of the macro-project.

Throughout this project, we developed written and verbal communication skills, reinforcing the use of another language. We developed social and interdisciplinary skills by establishing relationships with professionals from other research areas. This project addresses a problem that has not been considered previously in Colombia. We also acquired knowledge in image processing and medical image analysis for the development of this project.

Figure 2: Components of the macro-project “Biomarkers in silico". In this final career project, we will address the construction of an atlas of the Latin population.

1.5 OBJECTIVES

1.5.1 *General Objective*

Create a Latin brain magnetic resonance image atlas using computer vision techniques.

1.5.2 *Specific Objectives*

1. Select relevant computer vision techniques and methodologies for constructing brain MRI atlases.
2. Develop a Latin brain magnetic resonance image atlas using relevant computer vision techniques.
3. Define a set of criteria for evaluating the proposed brain atlas.
4. Evaluate the proposed Latin brain MRI atlas.

1.6 SCOPE

This atlas will be built using T1-weighted MRI scans, taking into account characteristics of latin population in terms of variety of ethnics, age distribution, and gender. We will devise a methodology for constructing cerebral atlases of magnetic resonance images. The output of this project will not be an application or software for creating brain MRI atlases.

1.7 DOCUMENT STRUCTURE

This document is organised as follows. We revise the necessary concepts to understand this work in Chapter 2 and the main strategies to develop brain atlases, their limitations and advantages in Chapter 3. We describe intermediate and final pipelines for the construction of the brain atlas and we evaluate our proposed brain atlas quantitatively and present the results inChapter 4. Finally, in Chapter 5, we present the conclusions of this project and suggest future research directions.

2

REFERENCE FRAMEWORK

2.1 THEORETICAL FRAMEWORK

This chapter details relevant concepts involved in creating a brain atlas using magnetic resonance images.

2.1.1 *Brain atlas*

A brain atlas, or brain template, is an anatomical representation of a population, which results from combining scans of various individuals [14]. These images depict the morphology of the brain under "normal" or abnormal circumstances, hence providing grounds for understanding the brain anatomy and detecting structural abnormalities. Furthermore, atlases enable spatial normalisation and segmentation of brain structures, making them essential for medical image analysis (Fig. 3).

Brain atlases have been developed for a long time and using diverse imaging modalities, including T1w, T2w or PET to name a few. Although initially drawn by hand, recent technological advances have allowed researchers to digitise them. To date, there are regional, disease-specific, domain-specific and surface atlases, as well as, pediatric brain and ageing brain atlases [15].

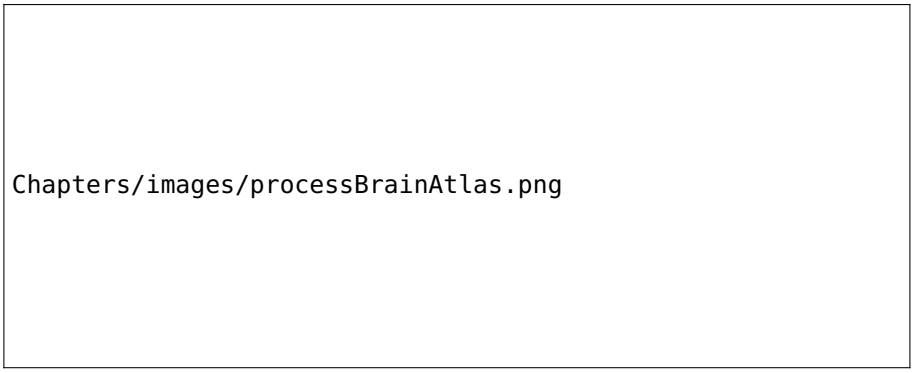

Figure 3: High-level schematic of the process of creating a brain atlas. First, we pre-process a set of magnetic resonance images with a specific population. This step includes intensity standardisation, skull stripping, noise correction and registration. Second, we register all images to a common space. Third, we average the images to obtain a brain atlas.

2.1.2 *Magnetic Resonance Imaging*

In this project, we will create a brain atlas out of magnetic resonance images from a healthy population. Thus, we first explain how these types of images are obtained.

MRI is one of the most commonly used imaging techniques in neurology and neurosurgery. It provides details of the brain, without requiring ionization or surgery. Also, it allows visualizing the brain anatomy in all three planes: axial, sagittal and coronal [37] (Fig. 4).

Figure 4: Three orthogonal views of the brain [34].There are three ways we can section the brain: the coronal, horizontal and sagittal planes.

Clinical MRI is based on the hydrogen nucleus due to the abundance in the human body and the magnetic resonance sensitivity (Fig. 5). For image formation, a large static magnetic field is used to perturb magnetic moments of proton from the equilibrium and measuring how perturbed moments relax back to equilibrium. After a time period the emitted signals are measured. Fourier's transformation is used to convert the frequency information contained in the signal from each location in the imaged plane to corresponding intensity levels, which are then displayed as shades of grey in a matrix arrangement of pixels [3]. As a result, it is possible to obtain different images types of the same body: T1-weighted, T2-weighted, and proton density weighted.

We will use T1-weighted images in this project as they provide sufficient contrast between brain tissues and fluids in the brain (Fig. 6).

Figure 5: MRI image formation process [4]. BO is the magnetic field that causes the hydrogen protons to change from being randomly moving to being aligned in parallel. Once that is done, the signal is measured and it is then represented in a gray level in the MRI.

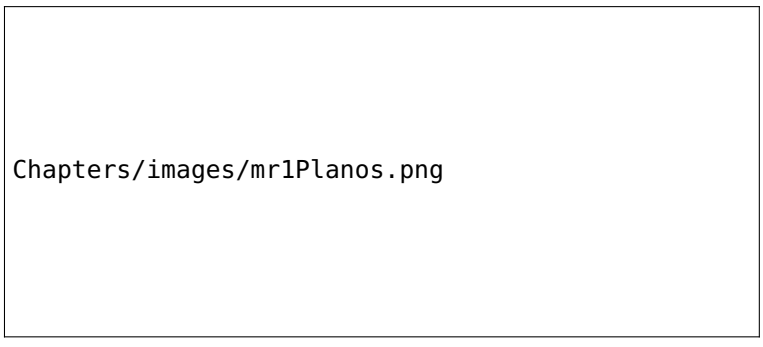

Figure 6: A T1- weighted magnetic resonance imaging in different planes: coronal, axial and sagittal, respectively. T1-weighted images are characterized for having light white matter and dark cortex on the gray scale.

2.1.3 *Stereotactic space*

Accurate mapping between the real world and the digital world is needed, especially in brain surgery where atlases are often utilised. This mapping between coordinate systems is known as the stereotactic space. This concept is of particular relevance at the moment of the atlas construction since all images must be in the same coordinate system. However, in most cases they are not, requiring spatial normalization to correct this.

2.1.4 *Spatial Normalization*

According to Johnstone et al [24], spatial normalisation involves deforming a brain image in a way that it fits a standardised brain image, to remove global differences in the size and orientation of each “normalised" brain and the same anatomical regions in each image occupy the same voxels, with attendant reduced statistical variance and increased power (Fig. 7).

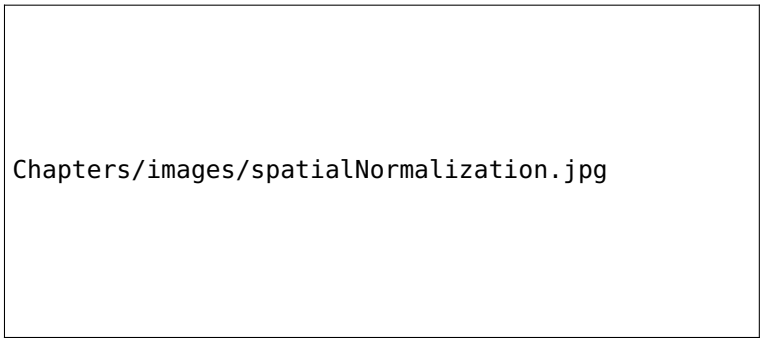

Figure 7: Midsagittal images of the same brain spatially normalized using ICBM152 template (Left) and the Talairach method (Right). Upper and lower dotted lines show differences [27]

2.1.5 *Intensity standardisation*

The construction of a brain atlas requires averaging a set of images voxel-wise. This implies that images should have the same range of intensities, a concept alluding to a value in the gray scale which lies in each voxel of the image, to avoid negative effects on subsequent processes [5]. Nonetheless, magnetic resonance imaging is sensitive to intensity alterations, leading to intensity variations even in images of the same subject obtained in a brief period of time (Fig. 8). Even though the lack of a standard intensity scale may have no direct impact on medical diagnosis made by experts, it compromises computational assessments [11, 7].

Intensity standardisation thus seeks to compensate for this problem. The main idea consists of transforming intensity values in such a way similar regions of interest in different patients exhibit similar intensities. While there are many methods for intensity standardisation, their advantages and disadvantages for the problem at hand are crucial for obtaining desired results [7].

Figure 8: MRI studies of the same person, taken with the same resonator within a short period of time between acquisitions. Even with the above conditions, the scans are likely to have different intensity values at the same point on the scanners as shown in the picture. In order to bring both images to a common scale, we apply intensity standardisation methods.

2.1.6 *Image registration*

Having the MRI scans in the same coordinate system is only a step towards constructing a brain atlas. Since brains are unique, there are variations in size and shape, as well as the variations induced at the moment of image acquisition in the resonator. Therefore, it is necessary to register them to ensure a correct alignment. Image registration consists of normalising multiple images spatially. In medical imaging, registration enables combining data from multiple modalities to obtain complete information about a patient [44].

2.1.6.1 *Registration based on nature of the transformation*

Registration techniques can be classified based on the nature of their transformation into: rigid, affine, projective, and curved transformations [2].

RIGID REGISTRATION Image registration maps and transforms a source image to corresponding a target image. This transformation is based on different parameters as translation, rotation, zoom and shear [2]. Rigid registration considers only rotation and translation, i.e. requires estimation of six parameters (three for image translation and three for image rotation). The scale of the input image remains the same and there is no local deformation involved, as illustrated in Fig. 9. An example of rigid registration is shown in Fig. 10.

(i) (ii) (iii) (iv)

Figure 9: Example of linear registration of an MRI from [12]. From left to right: i) Target image, ii) Image in which linear registration will be made, iii) Shows in red how (ii) would look superimposed on (i) and iv) shows how the linear registration would look.

AFFINE REGISTRATION This technique is one of often used as it involves rotation, translation, scaling and shearing, giving a total of twelve parameters to estimate. An example of affine registration is shown in Fig. 11.

PROJECTIVE REGISTRATION Projective transformation differs from affine transformation in the omission of collinearity of objects [2]. This technique has reference points that help defining objects in geometric space, which always seem to be quadrilateral. It is common to notice a change in the point of view of the processed against the target image, even if its dimensions are not changed the angle could be [2]. This approximation is not common for medical image analysis.

CURVED REGISTRATION Curved or elastic registration, unlike previous techniques, is a non-rigid registration, meaning it deforms the image at a local level [2], see Fig. 12. Naturally, this involves estimating parameters for each voxel in the image, being more computationally demanding [35].

Figure 10: The figure shows the original image (first row) and the image obtained after a rigid registration (third row) using as a target the linear atlas ICBM452 (second row). It is possible to appreciate that its dimensions in size do not change, however its localisation does. These images are part of a public data set from the UCLA Consortium for Neuropsychiatric Phenomics LA5c Study.

Figure 11: The figure shows the original image (first row) and the image obtained after performing an affine registration (third row) in order to target the linear atlas ICBM452 (second row). It is possible to appreciate that its dimensions in size change as well as its spatial location. These images are part of a public data set from the UCLA Consortium for Neuropsychiatric Phenomics LA5c Study.

Figure 12: Process of image Registration from [10]. The registration process of an image that has a point in the plane as reference is shown. Step A is the original image. Step B shows original image with pixels. Step C represents the transformation. Note that in step D, a rotation process is applied to the image in the linear registration, this can be seen in image E. The same process shown using a non-linear registration in image F is shown where image deformation can be appreciated.

2.1.6.2 *Registration based on domain of the transformation*

Registration techniques can also be classified based on the domain of the transformation into local or global [2].

LOCAL REGISTRATION In local registration, mapping between the source and target image is performed at pixel level, it resolves the geometric differences between source and target images by mapping the local corresponding areas [2]. This type of registration is appropriate in a situation when there are enough control points in the images. The obvious drawback of this technique is its increasing computational cost [2], compared to global registration.

GLOBAL REGISTRATION Global registration transforms the parameters of an image as a whole, and any change in the parameters affects the entire image [42].

3

STATE OF THE ART

In this chapter, we review and describe brain atlases that have been devised throughout the years [29]. Note we used the terms "brain atlas" and "brain template" interchangeably as they are referred as both in the literature [14]. For the state-of-the-art, we focused on T1w type MRI atlases, however, we included a non-digital atlas, which motivated the development of more of these.

3.1 TALAIRACH AND TOURNOUX ATLAS

Tailarach was among the first researchers to create brain atlases, developing three - one in 1957, a second one in 1967 and a third one in 1988 with Tournoux [32]. Tailarach and Tournoux built a brain atlas from two series of sections from a single postmortem brain of a 60 year old French woman [13] (Fig. 13) and provided a standardized set of coordinate system using the AC-PC line as reference, allowing to identify specifics locations in the brain. Although woefully inadequate as an anatomic reference [43], this manual atlas is still one of the most influential atlases in brain imaging [15] and has encouraged the use and further development of spatial normalization schemes to reduce size and shape variability of brains.

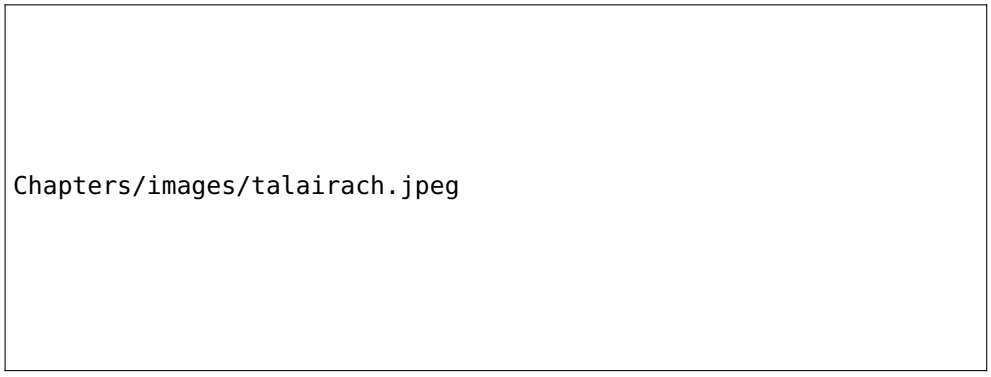

Figure 13: Orthogonal views of the Talairach and Tournoux manual brain atlas [16].

3.2 MNI 305

The Montreal neurological institute (MNI) has developed multiple brain atlases to provide an MRI base template that allowing automated registration. The first widely used MNI template

was MNI305, created in 1995 [36]. This atlas was created from a set of 305 T1-weighted MRI scans of relatively young participants (22% females and 19-28 years of age) [29]. The methodology consisted of three steps. First, the MNI team manually identified landmarks in 250 images and found the transformation that match them to the AC-PC line of the original Talairach atlas. Second, they used these transformations on the whole images and averaged the results to construct the MNI250 template. Third, the 55 remaining images were mapped to the MNI255 to reduce errors, then were averaged to obtain MNI305 [15]. Note the quality of MNI305 brain atlas is limited by the resolution of the input images [20] (Fig. 14).

Figure 14: Three orthogonal view of the MNI305 brain atlas [1]. Constructed with 305 MRI and a rigid registration, the population involve was between 19 to 28 years old.

3.3 COLIN 27

The Colin27 Brain atlas was created by the MNI in 1998 [15]. This average data set was created in a two-step process. First, 27 T1-weighted scans were linearly registered to the MNI305 and averaged to create an initial average. This average volume was used as a target for the second phase of registration where each original T1-weighted MRI was re-registered in stereotactic space. This procedure has the advantage of removing the small variance in intra-subject mapping in stereotactic space associated with the use of a multi-subject average [9].

The sample size used for building the Colin27 atlas meant it was not able to capture anatomical variability and was, to some degree, a reversion to the Talairach approach [15]. Nevertheless, Collin27 was adopted by various groups as a stereotactic template [15].

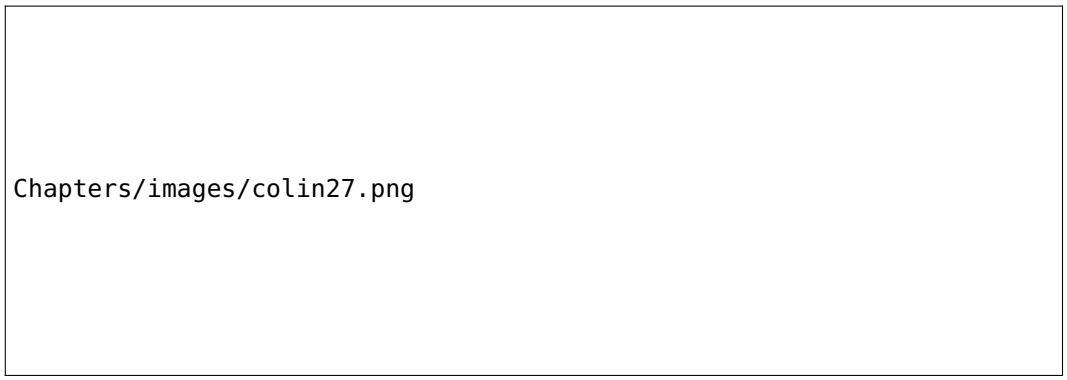

Figure 15: Colin27 is a stereotactic average of 27 T1-weighted MRI scans of the same individual [9]. Colin27 is a high-resolution MRI brain template [29]. However, it did not capture anatomical variability in a population [15].

.

3.4 MNI 152

The MNI 152 brain atlas was created in 2001. As its name suggests, 152 T1-weighted MRI images of a normal young-adult population were used for its elaboration. The construction procedure consisted of aligning all 152 images to a target one using a nine-parameter linear transformation and an additional non-linear registration to reduce inter-subject anatomical differences in shape, size, and orientation [29]. Unlike the MNI 305, this atlas provided full head coverage and more detailed information from the top of the brain to the bottom of the cerebellum [27] (Fig. 16).

MNI152 is popular worldwide being used in software packages, such as the statistical parametric mapping package (SPM) and the expanded FMRIB Software Library (FSL), and adopted by The International Consortium for Brain Mapping (ICBM) as standard template [29].

Figure 16: MNI152 Brain atlas, created with 150 MRI volume images from a normative young adult population. T150 MRI volume images from a normative young adult population [17]

3.5 ICBM 452

The ICBM 452 atlas is an average of T1-weighted MRI of normal young adult brains created in 2003 [29] (Fig. 17). The atlas space is not based on any single subject. Instead it is an average space constructed from the average position, orientation, scale, and shear from all the individual subjects. The atlas, therefore, is both an average of intensities and of spatial positioning [8].

ICBM 452 has two versions [8]. One is Affine AIR 12 Atlas, which is based on linear transforms of the subjects into the atlas space using a 12-parameter affine transformation. This atlas uses chirp-z interpolation for reslicing the voxel intensities [8]. And the second one is Warp 5 Atlas. This atlas is based on a fifth order polynomial transformation into the atlas space. Wrap 5 uses a 3D-sinc interpolation with half-windows of six voxels in each dimension. It has a more accurate alignment then the linear atlas and shows more detail [8].

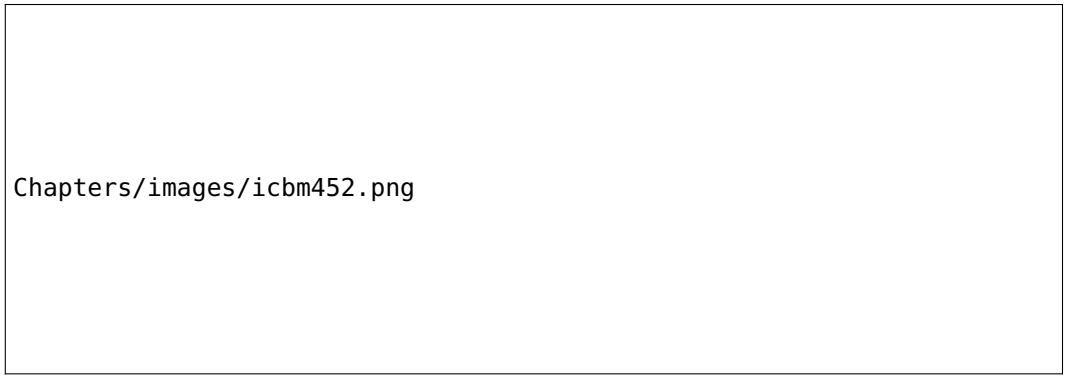

Figure 17: The three orthogonal views of the original ICBM 452 T1 atlas [30]. This atlas was performed with an rigid registration (affine) and 305 MRIs and almost half of them were duplicated to improve the results, to a total of 452 MRIs.

3.6 CHINESE56

This atlas was created with the purpose of make a comparison between Caucasian and Chinese population. It was created in 2010 and called Chinese56 alluding the 56 structures that were detected to perform the comparison. In the construction, thirty-five Chinese male subjects participated, all of them ranged in age from twenty-two to twenty-seven years. There were three steps for the atlas construction. First, construct an average template using Average Minimum Deformation Target (MDT). Second, perform a linear registration with the MDT as target image. Third, with the average obtained in step two, perform a non-linear warping to co-register all data sets [41].

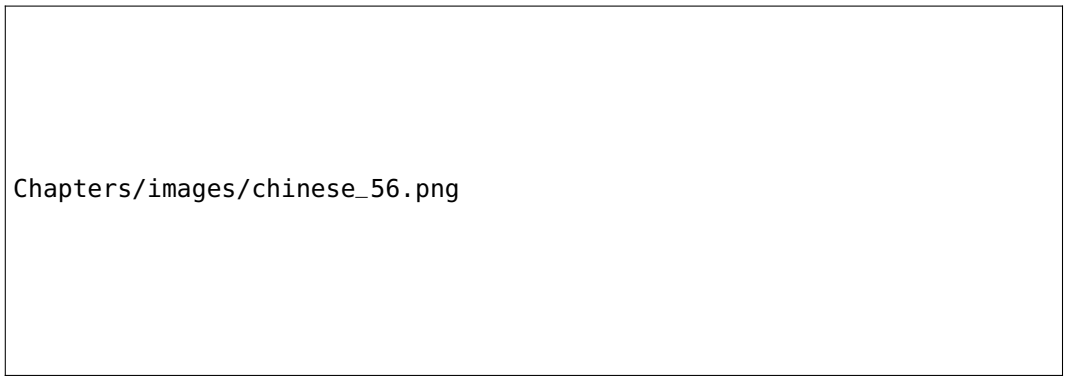

Figure 18: The three orthogonal views of the stereotactic representation of the Chinese whole brain template (Chinese_56) [41]. As a result of the project Chines56 atlas, was found how that global and regional anatomical brain measurements are significantly different between the Chinese and Caucasian populations (ICBM and MNI atlases) [41].

3.7 IBA100

In 2019 was constructed the IBA100 atlas from 100 (M/F=50/50) healthy adults T1-w MRI, between twenty-one and thirty years. The atlas was created using a nonrigid group-wise registration method, with the AC-PC line as reference for the registration, using the ANT's toolbox. This method aids in the derivation of an optimal atlas which is unbiased with respect to both shape and appearance in the diffeomorphic space [39]. From the resulting pipeline were also created two specific gender atlases for Indian population as well as the white and gray matter masks and CSF.

Figure 19: The Indian brain atlas (IBA100) in the three different slices. [39]. As same as the Chines56, the atlas-based comparison, in the Indian atlas project, indicated a significant difference between the global size of Indian and Caucasian brains. This difference was noteworthy for all three global measures, namely, length, width, and height [39].

3.8 CHINESE2020

The Chinese 2020 [31] atlas was published in 2015. This project seeks to improve the results obtained in the study carried out for the creation of the Chinese56 atlas , where there were limitations in terms of the number of studies, the focus of the area of interest and the participation of the female population and the elderly. This atlas involved a total of 2020 MRI studies at the beginning, however, due to noise, many were discarded leaving a total of 1081. This study was divided into 12 atlases sectioned by the age of the population, in 5-year intervals, from 20 to 75 years old. For image pre-processing, bias field correction, histogram matching and automatic Noise estimation Method were used. For the construction of the atlas, a linear registration was used between the images of each group using ANTs, followed by a non-rigid registration between the 12 atlases to obtain the atlas of the whole population. They also provide a rigid atlas with all age ranges which they use to define the stereotactic space of the Chinese brain.

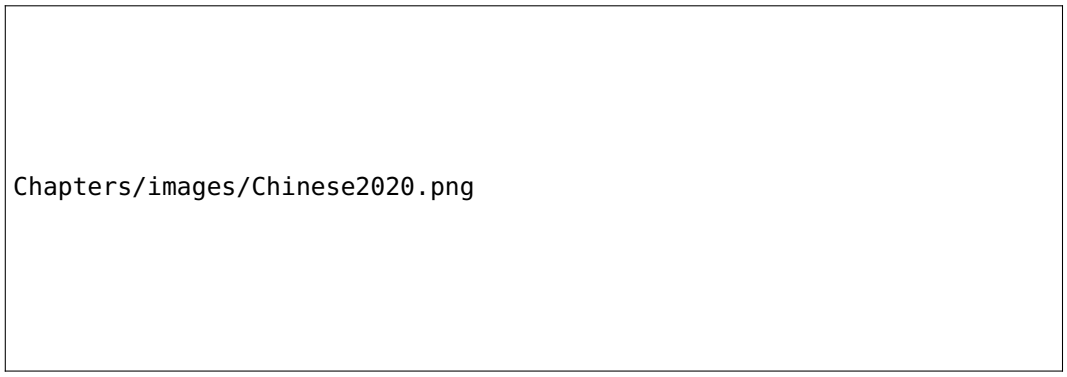

Figure 20: The three orthogonal views of the stereotactic representation of the Chinese whole brain template (Chinese2020) including the skull [31].

3.9 KNE 96

The Korean atlas KNE: Korean normal elderly brain tem-plate, is a brain atlas designed for the elderly with normal cognition population of Korea. The study was conducted in 2016. They used 96 T1 MRI studies (M=48, F=48). All participants were aged 60 years or older. For atlas construction they used the DARIEL toolbox in SPM8. For the validation of the atlas they used 48 MRI studies (M=24, F=24) compared the results of an image registration-induced with the Korean atlas and the ICBM152. Using the magnitude of the displacement vectors and the determinant of the Jacobian matrix, they were able to quantify the deformation produced. The study concluded that the values obtained from the validation were much

lower using the KNE96 than the ICBM152, making the local atlas better suited for studies in the same population [28].

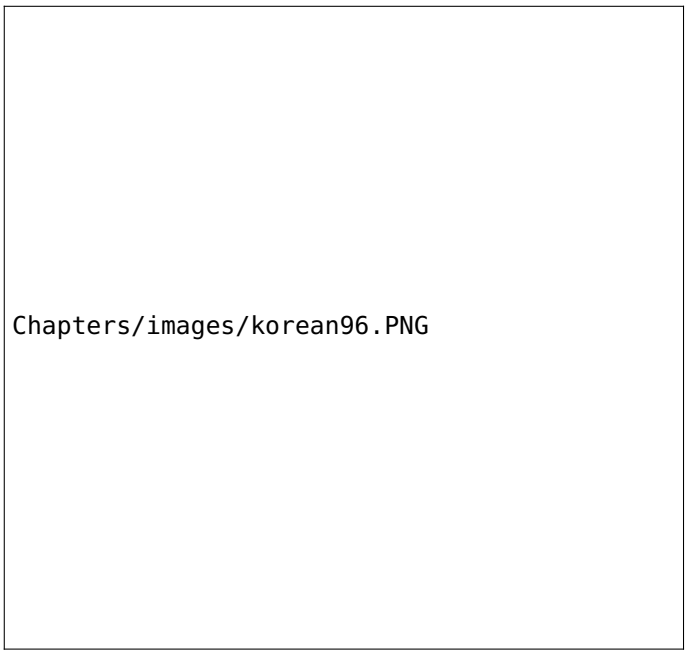

Figure 21: The three orthogonal views of the stereotactic representation of the Korean whole brain template (KNE96). [28]. The original MRI with the atlas was not found.

3.10 SUMMARY

In this chapter, we described a few brain atlases that have been constructed over the years. For each of these, were mentioned factors as the methodology and the characteristics of the population used for the construction of the atlas (age, sex, participants). All this information was grouped in Table 1. It is important to point out that there is not yet a brain atlas of the Latin population. This problem is addressed in this final degree project.

For the construction of the atlas, considering the methods and parameters used in the state of the art, 43 MRI images (26F - 17M) will be used, similar to the atlases developed by the Chinese an Indian researches. Based on the literature review, it has been considered, at first, perform a skull stripping, then, the use of an intensity standardisation method, and an affine linear image registration of 12-parameters, intended to preserve the original shape of the brain in the resonance. According to the literature, there is not a clear method for brain atlas evaluation. However, a quantitative evaluation, described in **??**, of the atlas will be performed.

We have found a framework to guide the desired methodology for constructing the atlas proposed in this project.

Summarising the ideas for this methodology we would start with an image noise removal algorithm, which is not mentioned specifically in the literature on brain atlases. However, in digital image processing we found this step very helpful to avoid any misinterpretation by the computer due to the artefacts it may detect.

As mentioned in our reference framework, the intensity standardisation is a task that may not be critical to the human eye, but to the computer it can be. By doing so, we intend that a specific point in our images, with a specific intensity, is a standard measurement in relation to the other images.

The process continues with a skull stripping. we considered this important, because of the approach of our atlas. In order to have an atlas of our population, which meets the same usability characteristics as atlases currently found in clinics or in medical image processing tools, we aim to focus on internal structures and the cerebral cortex. Leaving out the skull would increase the margin of error during image processing.

Then, one of the most important stages of brain atlas construction, the registration. There are several options in the literature. Considering the most recent atlas investigations, we opted for an affine registration, although we plan to test more registration types in order to finally decide which one would be the better fit for our latin atlas. then a voxel-wise averaging and a spatial normalisation to the MNI space.

Figure 22: First approach to the methodology proposed in this work, based on the literature review for the creation of a linear atlas of the Latin population. In a large scale, there is a preprocessing stage, where the skull is extracted, noise is removed and intensities are standardised. Then there is a registration stage, where the selected one would be an affine registration to finally obtain a linear atlas.

Table 1: Human brain atlases developed between 1988 and 2020. SD: standard deviation.

ATLAS	YEAR	SUBJECTS (FEMALES)	POPULATION	AGE (SD)	IMAGE TYPE	DIGITAL?	REGISTRATION	TOOLS
Talairach & Tournoux	1988	1 (1)	French	60	2D	No	–	Manual construction
MNI 305	1995	305 (66)	Canadian	23.4 (4.1)	3D T1	Yes	Linear (Inter-subject)	ANIMAL
Colin27	1998	1 (0)	Canadian	28	3D T1	Yes	Linear & non-linear (Intra-subject)	–
MNI 152	2001	152	Canadian	–	3D T1	Yes	Linear & non-linear (Inter-subject)	ANIMAL
ICBM 452	2003	452	Canadian	–	3D T1	Yes	Linear & non-linear (Inter-subject)	–
Chinese56	2010	56 (0)	Chinese	24.5 (1.8)	3D T1	Yes	Linear & non-linear (Inter-subject)	BET, BrainSuit, LONI BrainParser, FLIRT, ITK
IBA100	2019	100 (50)	Indian	25.5 (4.5)	3D T1	Yes	Linear & non-linear (Inter-subject)	ART, MIPAV Tool, ANTs
KNE96	2016	96 (48)	Korean	69.8 (6.6)	3D T1	Yes	Linear & non-linear (Inter-subject)	DARIEL Toolbox in SPM8
Chinese2020	2015	1081 (559)	Chinese	43.3	3D T1	Yes	Linear & non-linear (Inter-subject)	N4ITK, SyN ANTs, HAMMER

4

ATLAS CONSTRUCTION

The use of an atlas as close as possible to the study population is essential to reduce bias in stereotactic analyses. Since none of the atlases available in the literature was built using data from Latin people, they may not reflect the Latin phenotype, causing problems in subsequent stages of analysis. We propose then the creation of a Latin MRI brain atlas which allows a better picture of the brain of the Latin population in general. We show the effect of different processing pipelines on the visual quality of the atlases.

4.1 MATERIALS AND METHODS

We build our Latin atlas using 35 normal MRIs T1-weighted scans from the UCLA Consortium for Neuropsychiatric Phenomics LA5c Study data set [6] (n=35; 21 female). All the subjects in the sample have a normal diagnostic. The dataset is publicly available in https://openneuro.org/datasets/ds000030/versions/1.0.0. For the construction of the Latin atlas, we implemented a Python script which can be found publicly available at (`https://github.com/valeriarm/MRI-Brain-Atlas-Protocol`). To run this script is necessary a processor with the qualitives of a Intel core i5 8th gen or higher with more than 16GB of ram.

4.1.1 *Pre-processing*

The first step to be considered within our atlas construction pipeline is data pre-processing. This allows us to improve the quality of the image, reduce intensity variations, and, in general, effects that could compromise the quality of the atlas. Based on our literature review, these processes typically include noise removal, skull stripping, and intensity standardisation. However, we opted not to remove noise in the images as this process can get rid of subtle yet critical neuroradiological features.

4.1.1.1 *Skull Stripping*

Skull stripping consists of removing non-cerebral tissues, e.g. skin, fat, muscle, neck, and eye balls. Its accuracy and speed are therefore fundamental for any subsequent analysis, such as atlas construction and segmentation [25]. We opted for using ROBEX due to its consistent and improved performance on 137 scans acquired with different scanners and

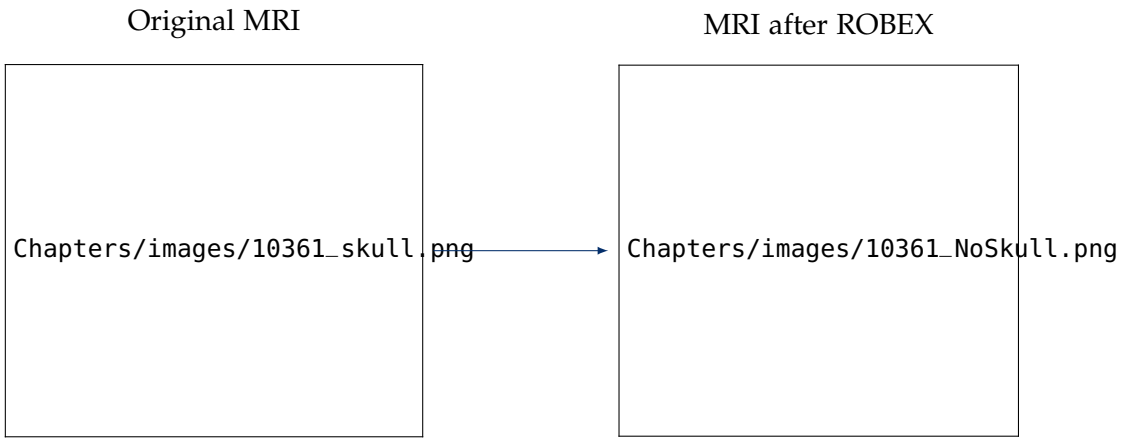

Figure 23: ROBEX skull stripping. ROBEX helped us to remove all the non-brain tissue in the MRI scans. In the images you can also see the bias field correction that this software performed.

imaging qualities compared to other skull stripping method [21]. Useful documentation on the usage of this tool was also a positive aspect that led to its selection.

4.1.1.2 *Intensity standardisation*

Intensity standardisation is also a key step considered in the construction of the latest atlases, IBA100 and Chinese56. An appropriate intensity standardisation method corrects for inter-scan intensity variations while preserving intensity ranks and being robust against biological abnormalities (e.g. brain atrophy and lesions), imaging artefacts (e.g. motion artefacts) and data harmonisation errors (e.g. skull stripping errors) [38].

We opted for a new method based on machine learning called DeLIS (https://github.com/emyesme/DeLIS) developed our research group that leverages spatial information and deep-learning based segmentation to produce better standardisation results when imaging conditions or tissue contrast are not optimal. Their deep learning based proposal produced similar or superior intensity standardisation results compared to traditional standardisation methods (z-score and histogram matching).

4.1.2 *Image registration*

The second step for creating atlases is image registration, which aligns all images to a characteristic or target image.

The literature suggests rigid registration is useful for this process [2]. We tried two approaches of rigid registration: six-parameter and nine-parameter rigid registrations which allow correcting for translation and rotation and translation, rotation and zoom, respectively.

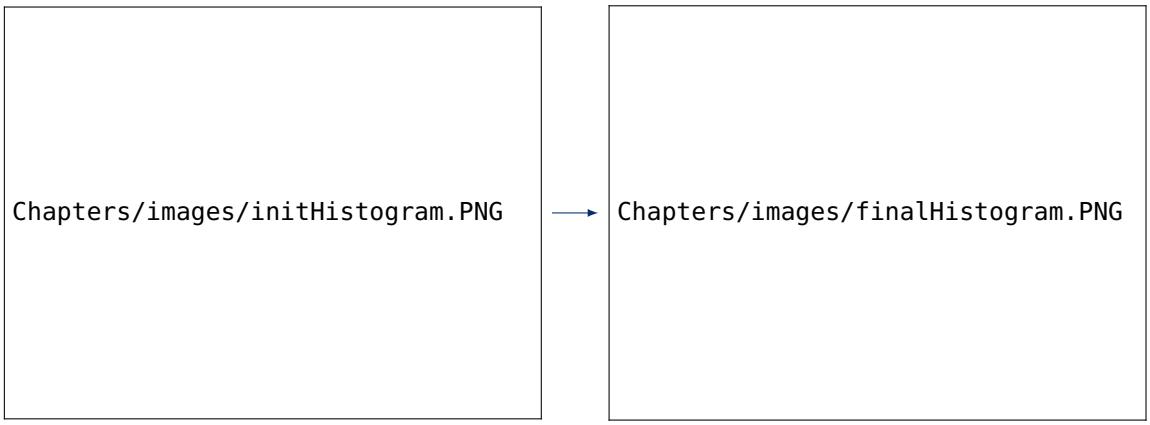

Figure 24: DeLIS Intensity Standardisation. The input is the histogram of a MRI scan already skull stripped and registered to the MNI space. The intensity values for this particular MRI range from $0-4000$. After apply DeLIS, the values are scaled on a scale from $0-1.2$.

We also considered affine registration as it corrects for translation, rotation, zoom, and shearing effects. We used FSL-FLIRT (FMRIB's Linear Image Registration Tool) for this task since it is a fully automated robust and accurate tool for linear, intra and inter modal, brain image registration of the FSL package [23, 22, 19].

Figure 25: Brain atlas made with 35 normal MRIs. We performed skull stripping of all brain scans using the tool ROBEX [21], which also performs a rough bias field correction. Continuing with the process we applied an intensity standardisation method called DeLIS [7]. The next step was to register the images, we opted for an affine registration. This was done with the FLIRT tool of FSL [40]. With all the images aligned, we created the atlas and using the same tool used to perform the affine registration, we carried out a linear registration to bring our atlas to the MNI space. Furthermore, we used a non rigid registration by ANTs to create a non-linear atlas.

4.2 QUALITATIVE ASSESSMENT

Several prototypes were made to build the atlas. We varied factors such as the cost function and the interpolation function, as well as the kind of image registration and the use or

not of an intensity standardisation method. We established some criteria to determine if the variations will be part of the atlas such as the shadows in the images (signal of a not adequate registration) and the definition for internal and external structures.

We tested two cost functions provided by FSL's FLIRT tool, corratio and normmi. We also tested the atlas by varying the image registration type with both cost functions. All prototypes are aligned to the ICBM452.

For the first prototype we used a 12-parameter affine register with the default cost and interpolation functions and without applying any intensity standardisation Fig. 26. However, when we created the second prototype Fig.27 with the same specifications plus DeLIS standardisation of intensities [7], we observed a slight improvement in the image definition. In Fig.28 we have a close-up showing this improvement.

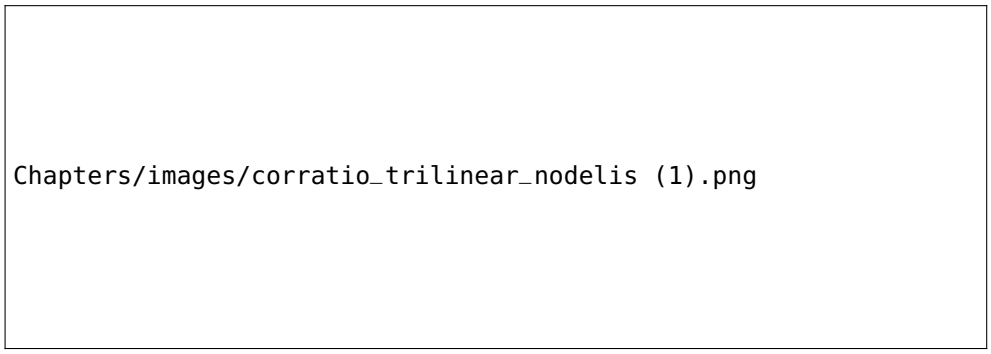

Figure 26: Brain atlas made with 35 normal magnetic resonance images[6]. An affine registration (12 parameters) with corratio as a cost function and trilinear interpolation (FSL FLIRT's default configuration). No intensity standardisation method is applied.

Figure 27: Brain atlas made with 35 normal magnetic resonance images[6]. An affine registration (12 parameters) with corratio as a cost function and trilinear interpolation (FSL FLIRT's default configuration). DeLIS intensity standardisation method was applied.

Figure 28: Zoom towards the area of the temporal lobe. Top left image is the Latin brain atlas without any standardisation method, in the close-up there are artifacts and lack definition in the appearance of the white matter. Bottom image is the atlas applying DeLIS, it shows a general enhancement improving the withe matter definition and reducing shadows.

Based on the results observed when applying the DeLIS method, we decided to continue to use it for the rest of our prototypes.

As mentioned, in the literature review it was found that the rigid image registration is the one used for atlas construction, for this we tested two configurations. In Fig.29 we can see the result obtained by applying a 6-parameter rigid registration. In Fig.30 result obtained by applying a 9-parameter rigid registration.

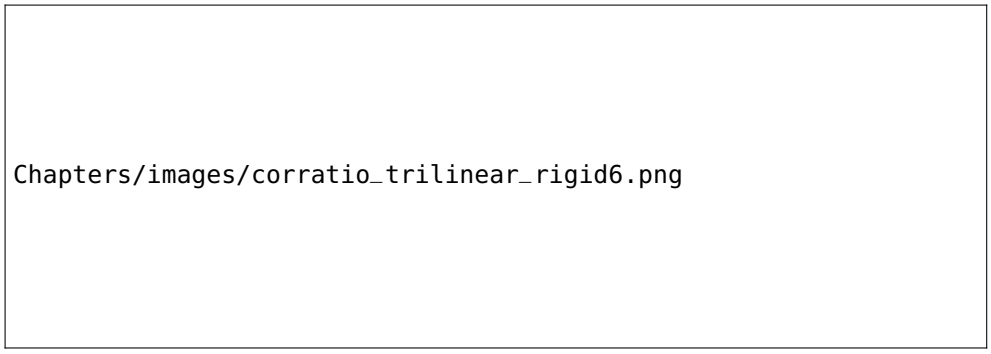

Figure 29: Brain atlas made with 35 normal magnetic resonance images. With rigid registration (6 parameters) using FLIRT and its default configuration.

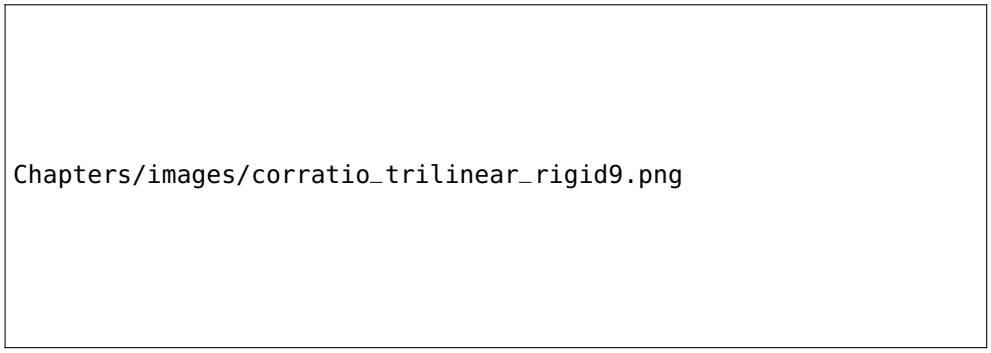

Figure 30: Brain atlas made with 35 normal magnetic resonance images. With rigid registration (9 parameters) using FLIRT and its default configuration. This prototype is larger than the one made with 6-parameter rigid registration because the use of the zoom helps the moving image to better fit the target image which in this case is the ICBM452 in the MNI space.

Although in the literature review it was found that a rigid registration is the one used for brain atlases construction, the results obtained by using either a 6 or 9 parameters are no better than those obtained with an affine registration. Accordingly, the following prototypes were constructed using that. In Fig.31 there is a better view of what was observed due image registration variations.

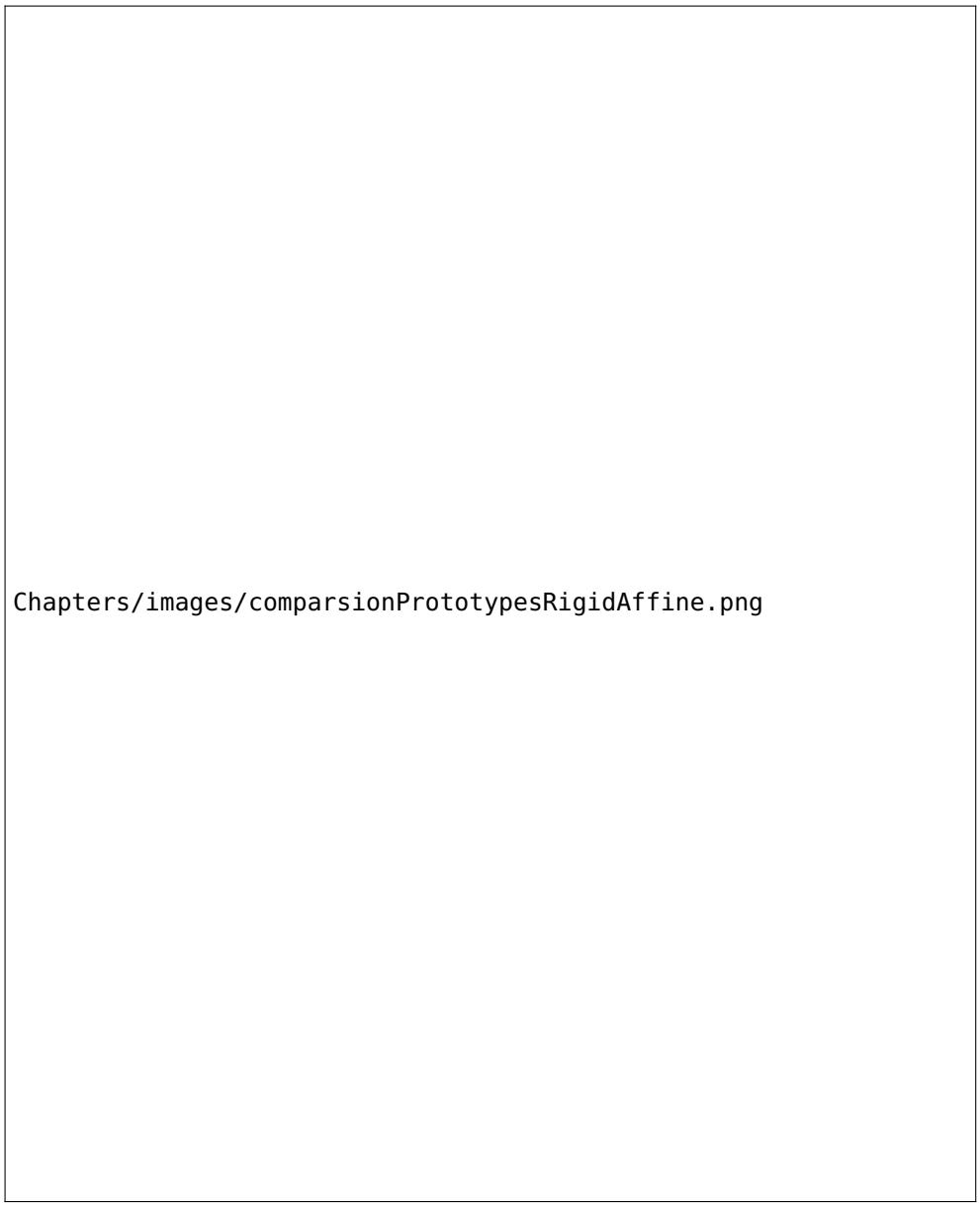

Figure 31: The images on the left side are the atlases with 6-parameter rigid, 9-parameter rigid and affine registration correspondingly (from top to bottom). The images on the right side are close-ups of the pons where it is possible to notice how for both rigid registrations, the definition of the edges of this structure is not well-defined and that the affine registration improves it.

In order to improve the atlas, we tried varying the cost function. For that we tried 4: corratio, normmi, leastsq and normcorr. The three fisrt are shown in Fig.32. Normcorr had almost the exact same result as leastsq which was not adequate for this particular data set, these two cost functions distort the original image.

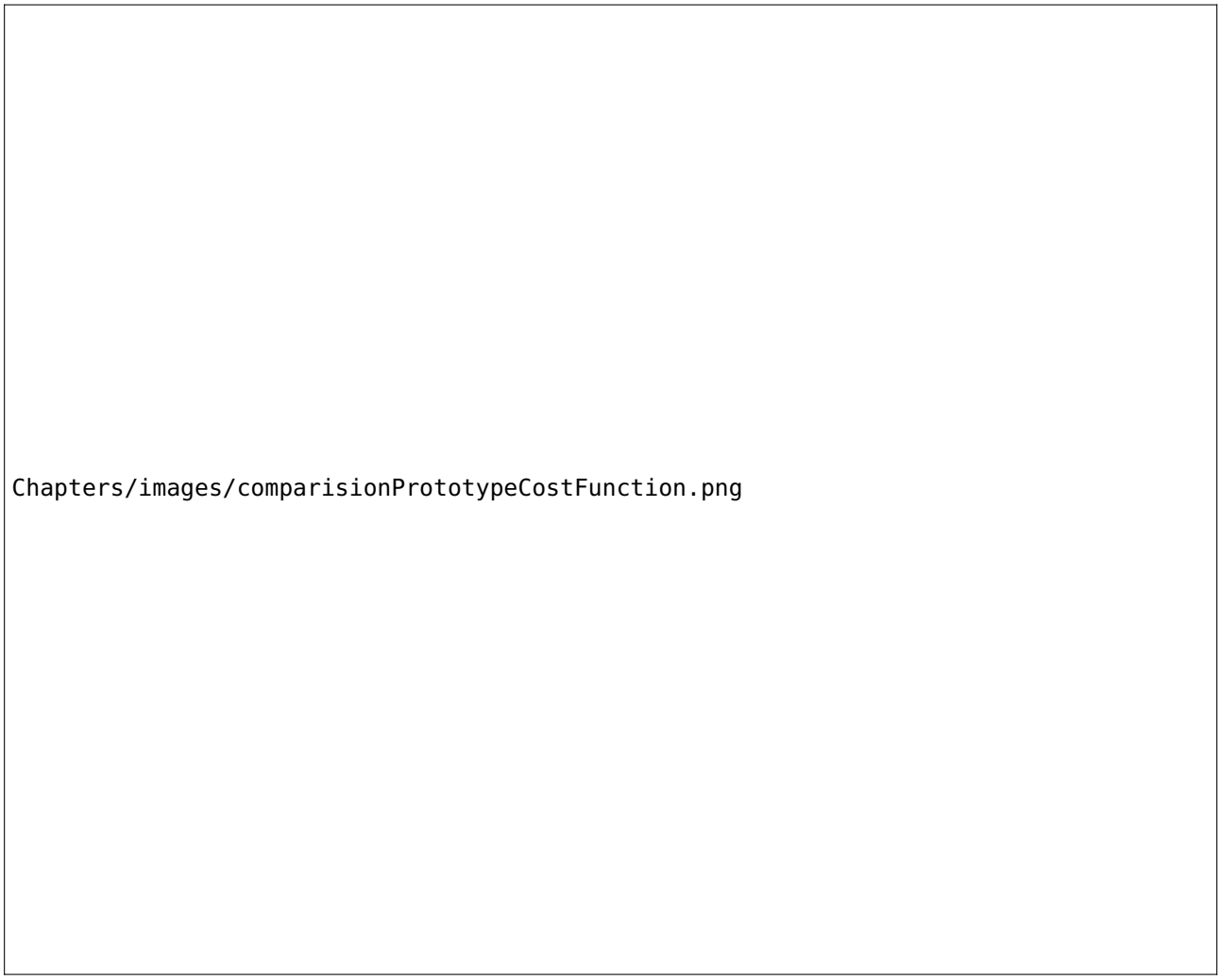

Figure 32: The first two rows of images are the prototypes using the corratio and normmi cost functions respectively. A better definition of the ventricle can be seen for the atlas made with the corratio function. The third row of images is the atlas made with the cost function leastsq, as we can see this function is not suitable to use for the image data set we have as it deforms the image. During the development of the prototypes we also tested the normmcorr function which had very similar results to leastsq so it was not shown in the image.

We crafted four prototypes using four interpolation strategies: trillinear (default), spline, sinc and nearest-neighbour. All of them had very similar results. Any interpolation function could, in this case, be used with this data set. We have decided to use the trillinear function, as it is the most commonly used and shows a slightly improvement against the others.

Figure 33: Brain atlas made with 35 normal magnetic resonance images from the UCLA Consortium for Neuropsychiatric Phenomics LA5c Study data set [6]. Includes intensity standardization and affine registration (12 parameters) with corratio as a cost function and four different interpolation approaches. Based on the results obtained from varying the cost function, better results were obtained using the corratio function. Therefore, different types of interpolation using this cost function were tested in the expectation of better results. The following interpolations were evaluated: trilinear (default), sinc, spline and nearest neighbour

Furthermore, we decided to make a prototype with a non-rigid registration, as was done in several atlas creation studies such as the Chinese 2020 [31] and the IBA100[39]. For its construction we used the prototype in Fig. 27 as a reference image to use ANTs (Advanced Normalization Tools) tool antsRegistrationSyNQuick. With this type of registration, an improvement in the sharpness of the cortex and a better definition of the internal structures can be appreciated.

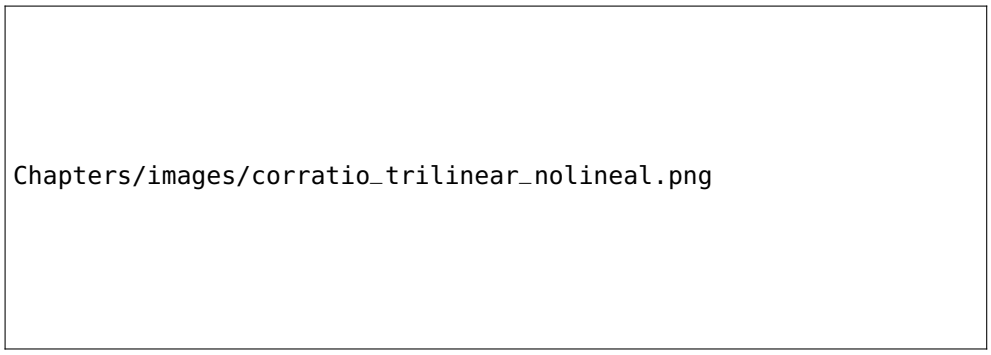

Figure 34: Brain atlas made with 35 normal magnetic resonance images from the UCLA Consortium for Neuropsychiatric Phenomics LA5c Study data set [6]. A non rigid registration was applied using ANTs (Advanced Normalization Tools) tool antsRegistrationSyNQuick. As a first step the prototype with affine registration was used as a reference image for the non-rigid registration, then the 35 images were registered with the tool antsRegistrationSyN-Quick. DeLIS intensity standardisation method was applied.

4.3 QUANTITATIVE ASSESSMENT

Literature around the evaluation of the atlases is not standardised in general. We considered two key aspects that could reinforce the idea of dissimilarities between brains. First, we measured global brain shape and sizes to compare the brains [41]. Second, we took advantage of the deformation fields to determine the extent to which our atlas represents a Latin person. Further details on these evaluations and the corresponding results on the following sections.

4.3.1 *Morphometric comparison*

We compared our developed atlas versus those available in the literature (Table 2). We used length, width, height, and volume of the whole brain as representative morphometric features [41]. An expert measured these on the Latin atlas.

We found differences between our atlas and currently available ones regarding the length, width, and height of the brain. Compared to the widely-used ICBM452 brain template, the Latin brain atlas is slightly shorter in length and height, and narrower in width. This finding suggest widely popular atlas templates (MNI305 [1], Colin27[9], ICBM452[8]) may not provide an optimal reference framework for processing brain images from the Latin population.

ATLAS	LENGTH (mm)	WIDTH (mm)	HEIGHT (mm)	AC-PC (mm)	VOLUME (dm^3)
Ours	175	135	92	27	1.66
Talairach	180	146	115	-	-
MNI305	181	142	111	28	2.39
MNI152	179	142	110	28	2.06
Colin27	176	141	114	27	2.07
ICBM452	176	144	109	28	1.56
IBA100	160	130	88	25	1.39
Chinese56	175	145	100	26	1.89
Chinese2020	162	137	94	26	1.51
Korean96	160	136	92	26	1.63

Table 2: Comparison of brain size and shape (Length, width, heihgt, AC-PC and volume) of the Latin atlas and other atlases

4.3.2 *Atlas validation by non linear registration*

We leverage non-linear registration to test the hypothesis of the existence of structural changes between populations (Table 3). Given that an atlas built using data from the target population would have better spatial coincidence compared to currently available ones, we expect deformation required via non-linear registration to be also lower. For this, the Jacobian matrix will be used, which allows us to appreciate the deformation that is necessary to apply for the base case to fit each of the atlases.

We found that the use of an atlas built from images of the target population requires less deformation compared to publicly available ones.

		OURS		IBCM452	
IMAGE	ICV (VOXEL)	TOTAL DEFORMATION	MEAN DEFORMATION	TOTAL DEFORMATION	MEAN DEFORMATION
10998	1′340,405.0000	374,892.6938	0.2796	458,591.9391	0.3421
11082	1′357,184.0000	288,640.1606	0.2126	381,485.7428	0.2811
11105	1′285,542.0000	251,273.3860	0.1954	391,736.0600	0.3047
11108	1′310,286.0000	253,528.0431	0.1934	364,030.2979	0.2778
11112	1′420,413.0000	346,086.2844	0.2436	470,897.3615	0.3315
11122	1′061,091.000	238,473.6855	0.2247	319,921.5752	0.3015
11142	1′486,594.0000	387,849.0568	0.2609	460,380.9530	0.3096
11156	1′335,382.0000	283,975.1458	0.2126	433,447.3927	0.3246

Table 3: Total and mean deformation per voxel in the intracranial volume (ICV) using our proposed atlas and the ICBM452.

5

CONCLUSIONS AND FUTURE WORK

5.1 CONCLUSIONS

Brain atlases – also referred to as brain templates – play a fundamental role in computational neuroscience as they provide a graphical representation of the average brain of a certain population. Growing evidence suggests the closer the atlas to the target population, the more the errors can be diminished in subsequent stages of the analysis. We test this premise on Latin subjects in this work.

During the course of this work, we identified a plethora of brain atlases. Among the most popular and commonly used are those developed by the Montreal Neurological Institute: MNI305, MNI152 or by The International Consortium for Brain Mapping: ICBM452. However, none of these corresponded to the Latin population we are dealing with, which could mean current analysis pipelines using currently available atlases may be suboptimal when dealing with Latin subjects.

In this project, we presented the construction and validation of a Latin brain template using T1-w MRI. The data[6] included a total of 43 studies (17M – 26F) ranged in age from 21 to 50 years. Our atlas was created using 35 volumes and it was validated on the remaining 8 subjects.

We found nine atlases in the literature constructed with similar characteristics to those we considered for our atlas, including the type of images, whether they were targeted to a specific population by age, disease or region. The methodology used for the construction of the atlas was guided by the methodologies used for the construction of more recent atlases such as those created by China and India. We followed steps as intensity standardisation and skull stripping, as well as rigid atlas registration (affine registration).

For the validation of the results we did not find a defined pipeline, however, we followed some of the methods used in studies to build specific population atlases that we found in the literature review. We performed a quantitative validation, in which we compared the ICBM452 with ours and see which one requires the least amount of global or regional warping from native subject space to atlas space.

Validation results of our Latin brain atlas against ICBM452 indicated positive aspects when dealing with a new volume from Latin population. It requires less global deformation and there is more similarity in size at global and structural levels with our template relative to others. Indeed, these observations indicate that having population atlases creates a better

reference for brains from the same population than any other. This, in general terms, would indicate that if there were a study of the Colombian population that required a brain MRI atlas, that atlas should be created with images of the same population in order to obtain a better result.

There were some limitations to complete this project, such as the amount of images used (43), even though it is not known how many subjects are needed to build an optimal average brain template[31]. In addition to the difficulties that arose due to national strike and the health crisis caused by COVID 19, which led to delays in the delivery time of the fundamental material for this work and also the time availability of the specialists required.

However, the results are encouraging to motivate future work on building an atlas with a larger set of subjects, and demonstrates that it is necessary to conduct further research on alternative phenotypic characteristics, such as gender, age and disease, for better analyses of regional brain morphometry. These group-specific templates could replace the atlases that are commonly used by investigators and research tools. A population-specific brain atlas can increase the accuracy of the results.

5.2 FUTURE WORK

For future work, we expect to be able to implement this protocol to create atlases for specific populations, such as the Colombian population, using a more significant number of resonance images. We also expect to carry out some assessments that have been left pending due to difficulties in staff availability by COVID-19. In this work there was a limitation in terms of the health personnel involved in the validation, we were supported by a neurosurgeon and a neurosurgery resident. We are looking forward to extending the study with the participation of more experts. The aim is also to achieve a qualitative evaluation. First, a qualitative evaluation by neurologists, neuroradiologists and neurosurgeons. This would be a valuable contribution as we would have a more visual opinion of the quality of the atlas and its usefulness in the real world, as they are the ones who use this kind of tools.

REFERENCES

[1] Mni average brain 305 mr. http://nist.mni.mcgill.ca/?p=957.

[2] Fakhre Alam, Sami Ur Rahman, Shah Khusro, Sehat Ullah, and Adnan Khalil. Evaluation of medical image registration techniques based on nature and domain of the transformation. *Journal of Medical Imaging and Radiation Sciences*, 47(2):178 – 193, 2016. ISSN 1939-8654. doi: https://doi.org/10.1016/j.jmir.2015.12.081. URL http://www.sciencedirect.com/science/article/pii/S193986541500394X.

[3] Mohd Ali Balafar, Abdul Rahman Ramli, M Iqbal Saripan, and Syamsiah Mashohor. Review of brain mri image segmentation methods. *Artificial Intelligence Review*, 33(3): 261–274, 2010.

[4] Howard Barnard. Interaction of the nuclear spin with magnetic fields - human brain. https://www.barnardhealth.us/human-brain/b-interaction-of-the-nuclear-spin-with-magnetic-fields.html, Feb 2019.

[5] Jan-Philip Bergeest and Florian Jäger. A comparison of five methods for signal intensity standardization in mri. In Thomas Tolxdorff, Jürgen Braun, Thomas M. Deserno, Alexander Horsch, Heinz Handels, and Hans-Peter Meinzer, editors, *Bildverarbeitung für die Medizin 2008*, pages 36–40. Springer Berlin Heidelberg, 2008. ISBN 978-3-540-78640-5.

[6] R Bilder, R Poldrack, T Cannon, E London, N Freimer, E Congdon, K Karlsgodt, and F Sabb. "ucla consortium for neuropsychiatric phenomics la5c study", 2020.

[7] Emily E. Carvajal-Camelo, Jose Bernal, Arnau Oliver, Xavier Lladó, María Trujillo, and The Alzheimer's Disease Neuroimaging Initiative. Evaluating the effect of intensity standardisation on longitudinal whole brain atrophy quantification in brain magnetic resonance imaging. *Applied Sciences*, 11(4), 2021. ISSN 2076-3417. doi: 10.3390/app11041773. URL https://www.mdpi.com/2076-3417/11/4/1773.

[8] UCLA Brain Mapping Center. Icbm 452 t1 atlas. http://www.bmap.ucla.edu/portfolio/atlases/ICBM_452_T1_Atlas/.

[9] McConnell Brain Imaging Centre. Colin 27 average brain, stereotaxic registration model, original 1998 version. URL https://www.bic.mni.mcgill.ca/ServicesAtlases/Colin27.

[10] Ke Chen, Lok Ming Lui, and Jan Modersitzki. Chapter 15 - image and surface registration. In Ron Kimmel and Xue-Cheng Tai, editors, *Processing, Analyzing and Learning of Images, Shapes, and Forms: Part 2*, volume 20 of *Handbook of Numerical Analysis*, pages 579 – 611. Elsevier, 2019.

[11] Giorgio De Nunzio, Rosella Cataldo, and Alessandra Carlà. Robust intensity standardization in brain magnetic resonance images. *Journal of digital imaging*, 28(6):727–737, 2015.

[12] Johan Debayle and Benoît Presles. Rigid image registration by general adaptive neighborhood matching. *Pattern Recognition*, 55:45–57, 2016.

[13] J. Dervin. Co-planar stereotaxic atlas of the human brain 3-dimensional proportional system: An approach to cerebral imaging 1988j. talairich and p. tournoux mark rayport georg thieme verlag. stuttgart, new york 3 13 711 701 1 price dm 268. pp. 122. illustrations 130. *The Journal of Laryngology & Otology*, 104(1):72–72, 1990. doi: 10.1017/s0022215100111879.

[14] David Alexander Dickie, Susan D Shenkin, Devasuda Anblagan, Juyoung Lee, Manuel Blesa Cabez, David Rodriguez, James P Boardman, Adam Waldman, Dominic E Job, and Joanna M Wardlaw. Whole brain magnetic resonance image atlases: a systematic review of existing atlases and caveats for use in population imaging. *Frontiers in neuroinformatics*, 11:1, 2017.

[15] Alan C Evans, Andrew L Janke, D Louis Collins, and Sylvain Baillet. Brain templates and atlases. *Neuroimage*, 62:911–922, 2012.

[16] Ezekial. Transforming datasets to talairach-tournoux coordinates, Mar 2012. URL https://www.slideserve.com/ezekial/transforming-datasets-to-talairach-tournoux-coordinates.

[17] McGill Centre for Integrative Neuroscience. Atlases. https://mcin.ca/research/neuroimaging-methods/atlases/, 2012.

[18] Sandra González-Villà, Arnau Oliver, Yuankai Huo, Xavier Lladó, and Bennett A Landman. Brain structure segmentation in the presence of multiple sclerosis lesions. *NeuroImage: Clinical*, 22:101709, 2019.

[19] Douglas N Greve and Bruce Fischl. Accurate and robust brain image alignment using boundary-based registration. *Neuroimage*, 48(1):63–72, 2009.

[20] Colin J Holmes, Rick Hoge, Louis Collins, Roger Woods, Arthur W Toga, and Alan C Evans. Enhancement of mr images using registration for signal averaging. *Journal of computer assisted tomography*, 22(2):324–333, 1998.

[21] Juan Eugenio Iglesias, Cheng-Yi Liu, Paul M Thompson, and Zhuowen Tu. Robust brain extraction across datasets and comparison with publicly available methods. *IEEE transactions on medical imaging*, 30(9):1617–1634, 2011.

[22] Mark Jenkinson and Stephen Smith. A global optimisation method for robust affine registration of brain images. *Medical image analysis*, 5(2):143–156, 2001.

[23] Mark Jenkinson, Peter Bannister, Michael Brady, and Stephen Smith. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*, 17(2):825–841, 2002.

[24] Eve C Johnstone, David Cunningham Owens, and Stephen M Lawrie. *Companion to psychiatric studies e-book*. Elsevier Health Sciences, 2010.

[25] P Kalavathi and VB Surya Prasath. Methods on skull stripping of mri head scan images—a review. *Journal of digital imaging*, 29(3):365–379, 2016.

[26] Ron Kikinis, Martha Elizabeth Shenton, Dan V. Iosifescu, Robert W. McCarley, Pairash Saiviroonporn, Hiroto H. Hokama, Andre Robatino, David Metcalf, Cynthia G Wible, Chiara M. Portas, et al. A digital brain atlas for surgical planning, model-driven segmentation, and teaching. *IEEE Transactions on visualization and computer graphics*, 2(3): 232–241, 1996.

[27] Jack L Lancaster, Diana Tordesillas-Gutiérrez, Michael Martinez, Felipe Salinas, Alan Evans, Karl Zilles, John C Mazziotta, and Peter T Fox. Bias between mni and talairach coordinates analyzed using the icbm-152 brain template. *Human brain mapping*, 28(11): 1194–1205, 2007.

[28] Hyunna Lee, Byung Il Yoo, Ji Won Han, Jung Jae Lee, San Yeo Wool Oh, Eun Young Lee, Jae Hyoung Kim, and Ki Woong Kim. Construction and validation of brain mri templates from a korean normal elderly population. *Psychiatry investigation*, 13(1):135, 2016.

[29] Yonghong Li, Jianhuang Wu, Hongwei Li, Degang Li, Xiaohua Du, Zhijun Chen, Fucang Jia, and Qingmao Hu. Automatic detection of the existence of subarachnoid hemorrhage from clinical ct images. *Journal of medical systems*, 36:1259–70, 09 2010. doi: 10.1007/s10916-010-9587-8.

[30] Yonghong Li, Jianhuang Wu, Hongwei Li, Degang Li, Xiaohua Du, Zhijun Chen, Fucang Jia, and Qingmao Hu. Automatic detection of the existence of subarachnoid hemorrhage from clinical ct images. *Journal of medical systems*, 36(3):1259–1270, 2012.

[31] Peipeng Liang, Lin Shi, Nan Chen, Yishan Luo, Xing Wang, Kai Liu, Vincent CT Mok, Winnie CW Chu, Defeng Wang, and Kuncheng Li. Construction of brain atlases based on a multi-center mri dataset of 2020 chinese adults. *Scientific reports*, 5(1):1–7, 2015.

[32] Pravat K Mandal, Rashima Mahajan, and Ivo D Dinov. Structural brain atlases: design, rationale, and applications in normal and pathological cohorts. *Journal of Alzheimer's Disease*, 31(s3):S169–S188, 2012.

[33] John Mazziotta, Arthur Toga, Alan Evans, Peter Fox, Jack Lancaster, Karl Zilles, Roger Woods, Tomas Paus, Gregory Simpson, Bruce Pike, et al. A probabilistic atlas and reference system for the human brain: International consortium for brain mapping (icbm). *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 356 (1412):1293–1322, 2001.

[34] Fintan S. Nagle. Essentials of brain anatomy. URL http://fsnagle.org/brain_anatomy.html.

[35] Lars Kristian Nielsen. Elastic registration of medical mr images. *Bergen, Norway: Thesis in Computational Science, Department of Mathematics and Neuroinformatics and Image Analysis Group Department of Physiology, University of Bergen*, 2003.

[36] Russell A Poldrack, Jeanette A Mumford, and Thomas E Nichols. *Handbook of functional MRI data analysis*. Cambridge University Press, 2011.

[37] David C Preston. Magnetic resonance imaging (mri) of the brain and spine: Basics. URL https://casemed.case.edu/clerkships/neurology/WebNeurorad/MRIBasics.htm.

[38] Russell T Shinohara, Elizabeth M Sweeney, Jeff Goldsmith, Navid Shiee, Farrah J Mateen, Peter A Calabresi, Samson Jarso, Dzung L Pham, Daniel S Reich, Ciprian M Crainiceanu, et al. Statistical normalization techniques for magnetic resonance imaging. *NeuroImage: Clinical*, 6:9–19, 2014.

[39] Jayanthi Sivaswamy, Alphin J Thottupattu, Raghav Mehta, R Sheelakumari, Chandrasekharan Kesavadas, et al. Construction of indian human brain atlas. *Neurology India*, 67:229, 2019.

[40] Stephen Smith, Peter R Bannister, Christian Beckmann, Mike Brady, Stuart Clare, David Flitney, Peter Hansen, Mark Jenkinson, Didier Leibovici, Brian Ripley, et al. Fsl: New tools for functional and structural brain image analysis. *NeuroImage*, 13(6):249, 2001.

[41] Yuchun Tang, Cornelius Hojatkashani, Ivo D Dinov, Bo Sun, Lingzhong Fan, Xiangtao Lin, Hengtao Qi, Xue Hua, Shuwei Liu, and Arthur W Toga. The construction of a chinese mri brain atlas: a morphometric comparison study between chinese and caucasian cohorts. *Neuroimage*, 51:33–41, 2010.

[42] Arthur W Toga. *Brain warping*. Elsevier, 1998.

[43] Arthur W. Toga and Paul M. Thompson. What is where and why it is important. *NeuroImage*, 37(4):1045–1049, 2007. doi: 10.1016/j.neuroimage.2007.02.018. URL https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2227945/.

[44] Barbara Zitová. *Mathematical Approaches for Medical Image Registration*. 01 2018. ISBN 9780128012383. doi: 10.1016/B978-0-12-801238-3.99990-2.