

Morphometry of the human hippocampus from MRI and conventional MRI high field

Emilie Gerardin

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Emilie GERARDIN

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Directeur de thèse :	Olivier COLLIOT
Rapporteurs :	Christian BARILLOT Arnaud CACHIA
Examinateurs :	Nicholas AYACHE Emmanuelle CORRUBLE Jean-François MANGIN
Membres invités :	Marie CHUPIN Joan GLAUNES

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CHAPTER

INTRODUCTION

The hippocampus is one of the most fascinating structures of the brain. Phylogenetically, it is one of the oldest parts of the mamallian brain, having an archaic three-layer structure. In small mammals such as rodents, the hippocampus occupies an important portion of the brain. Somehow paradoxically, this archaic structure is crucial for cognitive functions that seem at the core of our humaneness: memory and temporal consciousness, i.e. the ability to remember our past and imagine our future [Dalla Barba, 2002]. Anatomically, the hippocampus is no less intriguing [Duvernoy & Cattin, 2005]. It is made of two convoluted sheets of gray matter that are folded one onto another: the cornu Ammonis and the dentate gyrus. The cytoarchitecture and connectivity of the hippocampus are also particularly rich with many distinct fields exhibiting distinct cell types, density and organization. Last but not least, the dentate gyrus of the hippocampus is one of the few brain areas where adult neurogenesis has been demonstrated, proving false the long held dogma that neurogenesis only occurs during development [Altman et al., 1962; Eriksson et al., 1998].

Magnetic resonance imaging (MRI) allows studying the anatomy of the hippocampus in vivo. Using segmentation procedures, which can be manual [Hasboun et al., 1996] or automatic [Chupin et al., 2009a], one can delineate the contour of this structure and quantify its volume. Volumetric studies have been performed in various pathologies in which the hippocampus plays a major role. For instance, in Alzheimer's disease (AD), hippocampal volumetry can distinguish AD patients and elderly controls with high sensitivity and specificity. In temporal lobe epilepsy (TLE), hippocampal volumetry allows detecting atrophy, which is suggestive of hippocampal sclerosis, and, when found, is associated with good postsurgical prognosis for patients. However, volumetry is a very crude and limited way to assess the structure of the hippocampus and cannot capture the full spectrum of abnormalities. This results both in limited insight on the nature of the alterations and in limited sensitivity to detect them. Indeed, in Alzheimer's disease, the sensitivity of hippocampal volumetry is much lower at the prodromal stage of mild cognitive impairment (MCI) than at the dementia stage. In temporal lobe epilepsy, hippocampal volume is "normal" in about 20% of patients and more sensitive methods are thus needed.

Therefore, it is important to propose models of hippocampal shape that can assess the full spectrum of its complexity. In the past years, a large number of approaches for analyzing the anatomical shapes have been proposed in the medical imaging and computer vision communities, with successful applications to different pathologies and brain structure, including the hippocampus. However, these approaches suffer from two limitations. First, many of them were designed for group analysis and not for the classification of individual patients which is necessary to assist diagnosis. Second, these approaches usually analyze the external shape of the hippocampus. This may limit their sensitivity and makes the interpretation of the detected changes difficult. In which subparts of the hippocampus do the changes occur: cornu Ammonis, subiculum, dentate gyrus? What is the nature of these changes: local gray matter loss, changes in convolution, in organization? This is due to the fact that only the external border of the hippocampus is visible on conventional anatomical MRI using T1-weighted sequences at 1.5T or 3T. On the contrary, ultra high-field MRI (7T and higher) provides new contrasts and increased spatial resolution, opening a new window on the internal organization of the hippocampus. These new images offer a completely different view of hippocampal anatomy and new shape models are needed to exploit them.

* *

This thesis is devoted to the development of shape models of the hippocampus and their application to different brain pathologies. These developments are made in two distinct contexts: whole-hippocampus morphometry using conventional MRI and shape models of hippocampal substructure using ultra-high field MRI.

We were first interested in the context of conventional MRI at 1.5T or 3T which is easily accessible and can be applied to large cohorts of subjects. Using these images, only the external border of the hippocampus can be segmented. As mentioned above, a substantial number of hippocampal shape analysis methods have been proposed. However, most of these approaches were designed for group analysis and not for the individual classification of patients. This limits their application to assist the diagnosis of pathologies such as Alzheimer's disease for instance. We thus proposed a method to automatically classify between patients with Alzheimer's disease or MCI and elderly controls, based on hippocampal shape features. In this approach, we modeled hippocampal shape with previously proposed descriptors, the spherical harmonics, which provide a flexible multiscale representation. These descriptors were combined with a support vector machine for automatic classification. We first evaluated the approach in a group of 23 AD patients, 23 MCI patients and 25 elderly controls (recruited at Caen University Hospital). We further evaluated the approach using a larger population of 509 patients from the ADNI database. This work was done in collaboration with Rémi Cuingnet who compared 10 methods for the automatic classification of AD patients. Finally, we present another application of morphometry to a neuropsychiatric disorder: Gilles de la Tourette syndrome. This work was done as part of the work of Yulia Worbe. Our contribution concerns hippocampal and cortical morphometry.

The second part of this thesis is devoted to the development of shape models for assessing the substructure of the hippocampus using ultra-high field MRI (7T and higher). We proposed a new approach for modeling the shape of the gray matter ribbon formed by cornu Ammonis and the subiculum (which we refer to as the hippocampal ribbon in the following). The hippocampal ribbon has a laminar organization: it presents as a convoluted sheet of gray matter, which is horizontally organized as a superposition of layers. This two-dimensional organization within the sheet suggests that, like the cortex, its thickness is a fundamental measurement to study its anatomy. It seemed thus natural to model its shape using a thickness measure and a central skeleton. To that purpose, we proposed a method to compute a skeleton for thin surfaces as well as a robust estimation of the thickness which is based on an original variational formulation. This was done by estimating a smooth vector field which goes through the ribbon. This approach relies on representations of such vector fields using the theory of Reproducing Kernel Hilbert Spaces (RKHS). It provides a proper regularization which prevents numerical instabilities usually present in skeletonization approaches. This point of view leads to a well-posed problem as well as to an effective maximization procedure. Thickness is then computed as the length of the streamlines from one boundary to the other, following the vector field. The methodology can be applied either to the full volumic segmentation (3D case) or separately to each coronal slice (2D case). An attractive feature of the approach is that, thanks to the use of RKHS norms, one obtains a diffeomorphic flow from the internal to the external surface. To validate this approach, we first created a very high resolution atlas (with nearly isotropic 300 mm resolution) of the hippocampal substructure. To that purpose, we manually segmented a postmortem hippocampal specimen that had been previously acquired at 9.4T at the University of Pennsylvania [Yushkevich et al., 2009] (images available for download on the internet). We then applied the approach to in vivo 7T acquisitions acquired as part of our collaboration with University of Minnesota.

* *

This thesis contains three main parts. Part I provides background information on the hippocampus and reviews existing shape analysis approaches. Part II is devoted to the study of whole-hippocampus morphometry from conventional MRI at 1.5T or 3T. Part III is focused on the morphometry of hippocampal substructure using ultra-high field MRI (in vivo 7T and post-mortem 9.4T MRI). These three parts are further organized as follows.

In part I, chapter 2 presents the anatomy of the hippocampus, its histological and cytoarchitectonic features, its connectivity and briefly describes its role in cognition and pathologies. Chapter 3 reviews existing approaches for shape modeling of brain structures.

In part II, chapter 4 describes the method for the automatic classification of patients with AD or MCI, using hippocampal shape features, along with a first evaluation on 71 subjects¹. Chapter 5 then presents the evaluation of the method on a larger population of 509 patients from the ADNI database². Chapter 6 then presents another application of morphometry to a

¹This chapter was published as a journal paper in NeuroImage [Gerardin et al., 2009]

²This was done in collaboration with Rémi cuingnet and was included in a journal paper in NeuroImage [Cuingnet et al., 2011]

neuropsychiatric disorder: Gilles de la Tourette syndrome³.

In part III, chapter 7 presents the construction of a very high resolution atlas of hippocampal subtructure. Chapter 8 gives a few elements on the theory of reproducing kernel hilbert spaces (RKHS). Chapter 9 presents the method for shape modeling of the hippocampal ribbon and thickness estimation. In chapter 10, we validate this approach using the postmortem atlas. Chapter 11 decribes the method used for template estimation at the group level, based on large deformation diffeomorphic metric mapping and currents. In chapter 12, we apply the approach to in vivo 7T MRI data.

³This chapter was published as a journal paper in Brain [Worbe et al., 2010]. This was part of the work of Yulia Worbe to which we collaborated.

PART 1

BACKGROUND



THE HIPPOCAMPUS

The hippocampus is a brain structure which plays a crucial role in fundamental cognitive processes like memory or emotions. It is also involved in different neurological and psychiatric diseases, such as Alzheimer's disease, epilepsy or depression. This chapter gives a comprehensive description of the anatomical structure of the hippocampal formation. It also provides a brief introduction to the role this structure plays in normal human brain function. Finally, it presents some pathologies in which the hippocampus can be damaged.

In the following, we will address aspects of the anatomy of the hippocampal formation. This is a difficult task, due to two major problems:

- the complexity of the hippocampal structure, both in terms of geometry and of histology.
- the large number of existing terminologies to describe the parts of the hippocampal formation.

The hippocampus, also referred to the hippocampal formation, is a region that includes the hippocampus proper, or cornu Ammonis, the gyrus dentatus and the subiculum. Hippocampal anatomy is complex, and it is hard to describe it only with words. Thus, we incite the reader to refer to the illustrations given in this chapter for a better understanding of its three-dimensional configuration.

The rest of this chapter is organized as follows. Section 2.1 presents the localization of the hippocampus within the medial temporal lobe of the brain. We then describe its overall shape (Section 2.2) and the anatomy of its macroscopic subparts (Section 2.3). Section 2.4 is devoted to the histological features of its inner structure. Section 2.5 presents its connectivity and its relationships with neighbouring structures. We then briefly summarize its role in cognition (Section 2.6) and pathologies (Section 2.7). Finally, we present the role of MRI in studying the hippocampus in vivo (Section 2.8).

2.1 Localization, or How to find the hippocampus without GPS

The hippocampus is a bilateral structure which belongs to the limbic system, a group of structures that works together to produce and regulate emotions and to form new memories. The hippocampus is phylogenetically one of the oldest structures in the mammallian brain, the hippocampi are thus situated deeply in both of the cerebral hemispheres. More precisely, each hippocampus belongs to the fifth circonvolution of the temporal lobe, and forms the medial wall and floor of the lateral ventricle. Thus, to locate the hippocampus, we have to look at the internal (medial) aspect of the hemisphere (figure 2.1).



Figure 2.1: Inferomedial aspect of the right hemisphere. The red arrow indicates the temporal pole, while the green arrow shows the emplacement of the hippocampal region. The hippocampus being a deep structure, only a small part of it is visible superficially. From [Duvernoy & Cattin, 2005]

To see the hidden part of the hippocampus and its whole shape, some overlying structures have to be removed; the result can be seen in figure 2.2.

An alternative solution is to observe sections of the brain, where the hippocampus and the surrounding structures can be more easily located. Coronal sections at the middle part of the hippocampus reveal its typical internal structure, as shown in figure 2.3.

2.2 General Shape, or The hippocampus to the naked eye

The hippocampus is a small elongated structure, and has a total length of between 4 and 4.5 cm. The classical gross anatomical image of the human hippocampal formation is a bow which anterior extremity is enlarged and which posterior extremity narrows like a comma. The general shape of the hippocampus is shown on figure 2.4.

It can be divided into three segments:



Figure 2.2: Dorsolateral view of the human hippocampus after removal of the overlying structures and opening of the lateral ventricle. From [Insausti & Amaral, 2004].



Figure 2.3: Coronal view of the hippocampus. The hippocampal region is circled in red. From [Duvernoy & Cattin, 2005].

- A head, or anterior segment, which is transversely oriented. It is the largest part of the structure. It shows elevations, the *digitationes hippocampi*.
- A body, or middle segment, which is sagittally oriented. The gyrus dentatus forms the axis of this elongated part.
- A tail, or posterior segment, whose organization is similar to that of the body, but with a transverse orientation.

It should be noted that, while the distinction between the head and the body could be



Figure 2.4: Intraventricular aspect of the hippocampus. H: head, B: body, T: tail, f: fimbria, s: subiculum. From [Duvernoy & Cattin, 2005].

easily made, from the enlargement of the structure in the uncal part, the transition between body and tail is more difficult to identify.

The term "hippocampus" (latin for sea horse) was given by the italian anatomist Arantius in 1587, and inspired by the three-dimensional form of the human hippocampus which reminds of this sea creature; the head and tail of the brain structure corresponding to those of the animal. The hippocampal shape also inspired other comparisons: the cornu Ammonis, or Ammon's Horn is named after the mythological Egyptian god (figure 2.5)



Figure 2.5: The Egyptian god Ammon, who inspired the name "cornu Ammonis".

Within this gross structure, the hippocampus is bilaminar, the two layers consisting of the cornu Ammonis (or hippocampus proper) and the gyrus dentatus. These two interlocking layers are visible in figure 2.6. They are separated from each other by the hippocampal sulcus.



Figure 2.6: General view of the internal structure of the hippocampus. The cornu Ammonis (**CA**) and gyrus dentatus (**GD**) form two interlocking, U-shaped laminae. 1: hippocampal body, 2: hippocampal head, 3 hippocampal tail, 4: digitationes hippocampi, 5: margo denticulatus. From [Duvernoy & Cattin, 2005].

[Kier et al., 1997] examined hippocampal development in normal fetal specimens using MR imaging, dissection, and histology, in order to explain the progressive infolding of the fetal dentate gyrus, cornu Ammonis and subiculum around the hippocampal sulcus. However, the explanation of this particular configuration remains uncertain: in early development, the two laminae are continuous, then as a result of the marked expansion of the neocortex and unequal growth of the various components of the hippocampus, the cornu Ammonis would fold into the ventricular cavity, forming the hippocampal sulcus. The gyrus dentatus becomes concave and seems to slip beneath the medial end of the cornu Ammonis. At the end, the two layers fit into each other, as shown in figure 2.7.

2.3 Topography, or The hippocampus through a magnifying glass

The next paragraphs describe the aspect of the hippocampus and the respective position of the two layers, in the three segments of the hippocampus, namely the body, head and tail. Figure 2.9 summarizes this complex anatomical construction.



Figure 2.7: Diagram in the coronal plane illustrates stages of infolding of the components of the left hippocampus. A : Early in fetal development, the dentate gyrus (**D**), cornu ammonis (**C**), and subiculum (**S**) are arranged serially along the temporal horn(**T**). B and C : gradual infolding of the components around the hippocampal sulcus that first forms between the dentate gyrus and cornu Ammonis (large arrow in A). The hippocampal sulcus (small arrow in Figure B and C) shifts later to a location between the dentate gyrus and subiculum, and eventually becomes obliterated. From [Kier et al., 1997].

Hippocampal body The hippocampal formation has its simplest shape in its body: the fields of the cornu Ammonis and the gyrus dentatus fold over each other and form the characteristic C-shape of the hippocampus. In coronal sections of the hippocampal body, we can see that the gyrus dentatus is a narrow, dorsally concave lamina. Its concavity envelopes the last segment of the cornu Ammonis. The hippocampal sulcus becomes vestigial, and the two layers are fused together (a few residual cavities may persist): it becomes impossible to distinguish between them. Only a small segment of the gyrus dentatus is visible, and bordered by the superficial hippocampal sulcus along its entire length. It exhibits various folds on the surface, these folds form the "teeth" or dentes of the gyrus (Figure 2.8). These rounded protrusions diminish in size caudally. The dentes are surface manifestations of general folding in the gyrus dentatus.

The hippocampal body is limited in its lateral part by the horn of the lateral ventricule. The white matter of the parahippocampal gyrus forms the inferior boundary, while the hippocampus is prolonged by the subicular region (the "bed" of the hippocampus) in its infero-medial limit. The hippocampal body is bordered medially by the fimbria. The fimbria is a narrow, white strip which more or less hides the superficial part of the gyrus dentatus. Note that the intraventricular hippocampal surface is almost entirely hidden by voluminous choroid plexuses; only the hippocampal head is devoid of these plexuses.

Hippocampal head As we approach the anterior limit of the hippocampal formation, its configuration becomes more and more complex. Prominent bulges, the digitationes hippocampi, or digitations, become visible in the hippocampal head. The term "pes (foot) hippocampi" is sometimes used for the digitationes hippocampi. There are usually three or four digitations, sagittally oriented and separated by small but definite sulci. In coronal sections, the digitations are seen to be transverse foldings of the cornu Ammonis. Each digitation is surrounded by a digital extension of the gyrus dentatus. These folds vary in thickness, as is frequent in cortical gyri in general. When the hippocampal digitations appear at the junction of the body and head, the fimbria gives way to a thick alveus which covers them.



Figure 2.8: Aspect of the hippocampus after opening of the temporal horn of the lateral ventricle. A small segment of the gyrus dentatus is visible. The arrow shows the superficial hippocampal sulcus and the dentes of the gyrus. From [Duvernoy & Cattin, 2005].

The hippocampal head is free of choroid plexuses. The anterior part of the hippocampus is adjacent to the amydgala. It is determined by a thin layer of white matter, namely the alveus. The temporal horn of the lateral ventricle may be visible between the hippocampus and the amygdala. The presence of white matter of the parahippocampal gyrus or the entorhinal area determines the inferior limit.

Hippocampal tail The tail is the most posterior part of the human hippocampal formation. At this level, the structure again loses its simple C-shaped organization. This segment is smaller than the hippocampal head, but its orientation and internal structure are relatively similar: although digitations do not appear at the surface of the tail, it is composed of a vast layer of the cornu Ammonis centered by the digital extensions of the gyrus dentatus. The distinction between the different fields becomes very complex at the most posterior segments. The fimbria, which in the initial segment hides the margo denticulatus, separates from it, ascending to join the crus of fornix. The extraventricular, superficial part of the hippocampal tail has relations similar to those of the body.

Because of the curvature of the hippocampus, the gyrus dentatus and the cornu Ammonis have the same reciprocal position in a coronal section of the body as in a sagittal section of the head or of the tail.



Figure 2.9: Coronal sections of hippocampus, and 3D diagrams, showing planes of section. A,B: Head; C: Body; D: Tail. The modifications of the respective positions of the gyrus dentatus and the cornu Ammonis can be observed from anterior to posterior levels. From [Duvernoy & Cattin, 2005].

2.4 Subdivisions, Histology : The hippocampus under the microscope

The different fields of the hippocampus have different histological characteristics. A thorough knowledge of hippocampal histology is necessary for a better understanding of its global shape and internal configuration, as well as its connections with the surrounding structures. In chapter 7, we will establish a coherent protocol of segmentation of the subfields of the hippocampus, and try to relate anatomical features to the underlying cytoarchitectonic structures.

2.4.1 Different types of cortex in the temporal lobe

We will start with a brief overview of the cytoarchitecture of the human brain.

The cerebral cortex is a highly folded sheet of grey matter encasing the brain, home to most higher cognitive functions. We can easily distinguish at least two types of cortices: the major component of the human brain is made of a six-layered cortex, the neocortex, while the olfactory cortex and the hippocampal formation are elements of the paleocortex, or allocortex, which consists of only three layers. Evolutionarily speaking, the three-layered organization is considered to be "older", so this type of cortex is also known as archicortex whereas the "newer" six-layered cerebral cortex is "neocortex"). The cortex adjacent to the hippocampus changes from three layers to six layers, this transitional zone is classified as mesocortex, or periallocortex, and includes the parahippocampal gyrus and the entorhinal region. These cytologically different types of cortex exhibit distinct patterns of architecture.



Figure 2.10: Laminar organization of the neocortex. The different layers contain different cell types. They are numbered from I to VI, from superficial to deep. From [de Economo & Koskinas, 1925].

Horizontal lamination of the neocortex The neocortex consists of various types of neurons, horizontally structured in layers, which differ by cell composition and density [Brodmann, 1909]. There are six layers, numbered from I to VI, from superficial to deep. Each layer is characterized by the neuronal cell types it contains and its connections with other cortical and subcortical regions. The cortical layers are illustrated in figure 2.10.

2.4.2 The cytoarchitecture of the hippocampus

The gray matter parts of the hippocampal formation (the cornu Ammonis and the gyrus dentatus) are covered by two white matter structures: the alveus and the fimbria. The hippocampus is composed of allocortex, a three-layered structure. Distinct organizations are identifiable in the cornu Ammonis and the gyrus dentatus.

Cornu Ammonis In the cornu Ammonis, the three layers (starting from hippocampal sulcus to alveus) are as follows:

- A molecular cell layer which contains apical dendrites of the pyramidal cells and a number of interneurons. This layer is usually divided into three distinct sub-layers: the stratum moleculare contains a few interneurons and dendritic connections to the pyramidal layer and is adjacent with the molecular layer of the dentate gyrus; the stratum lacunosum contains axons of the perforating fibers and the Schaffer collaterals, which run parallel to the surface of the cornu Ammonis, and the stratum radiatum contains mostly apical dendrites of the pyramidal cells.
- A pyramidal cell layer (stratum pyramidale), which contains the main cells of the cornu Ammonis: the pyramidal cells. Their dendrites extends into the molecular layer.
- A polymorphic layer (stratum oriens) which contains basilar dendrites of the pyramidal cells, and scattered neurons (basket cells). In humans, this layer merges with the stratum pyramidale.

Alternatively, a six-layered nomenclature of the hippocampus can be used, formed successively by the stratum moleculare, the stratum radiatum, the stratum lacunosum, the stratum pyramidale, the straum oriens, and the alveus.

The repartition of these layers varies along the cornu Ammonis. Thus, the cornu Ammonis can be divided into different sectors, using cytoarchitectonic criteria . A varying number of nomenclatures have been proposed, for example Rose [Rose, 1927] divided the cornu ammonis into five zones labeled H1 to H5. In the following, we will use the nomenclature introduced by Lorente de No [Lorente de No, 1934]. He described four fields of pyramidal cells, dividing the hippocampus into four fields and labeled them CA1-CA4. However, it should be noted that some imprecisions persist in the definition of the limit of these fields. Borders between the various fields of the hippocampal formation are especially difficult to establish in humans compared to other species. This is due, in part, to the overlapping of neuronal layers at the interfaces of fields.

CA1 is the largest sector of the cornu Ammonis and is continuous with the subiculum. It contains small scattered pyramidal cells, with triangular somata. CA2 consists of a narrow band of densely packed pyramidal cells, with ovoid somata. The curve, or genu, of the cornu Ammonis (where it enters the concavity of the gyrus dentatus) is a densely packed stratum of pyramidal cells, and is designated as CA3. Its pyramidal somata are similar to those in CA2, but density in CA2 is greater. A specificity of CA3 is the presence of the stratum lucidum, a supplementary layer which contains fine, non myelinated fibers, the mossy fibers, that originate in the dentate gyrus. CA3 continues within the concavity of the gyrus dentatus; this field is designated as CA4. CA4 contains scattered, large ovoid pyramidal cells and intertwined large and myelinated fibers.

Gyrus dentatus The dentate gyrus fits inside the hippocampus. It is a trilaminate cortical structure. The three layers (starting from the stratum moleculare of CA to CA4) are as follows:

• A molecular layer (stratum moleculare) which is relatively cell free. It contains dendrites of granule cells.



Figure 2.11: Diagram and 9.4T MRI view of the structure of the hippocampus (coronal section). Cornu Ammonis: 1 =alveus, 2 =stratum oriens, 3 =stratum pyramidale, 3' =stratum lucidum, 4 =stratum radiatum, 5 =stratum lacunosum, 6 =stratum moleculare, 7 =and 7' =vestigial hippocampal sulcus. Gyrus dentatus: 8 =stratum moleculare, 9 =stratum granulosum, 10 = polymorphic layer, 11 =fimbria. From [Duvernoy & Cattin, 2005].

- A granule cell layer (stratum granulosum), the main layer of the gyrus dentatus. It is a thin layer, comprised of densely packed granular neurons, which have small round bodies. Efferent neurons from the granule cells are mossy fibers that synapse only with cells of hippocampal areas CA2 and CA3.
- A polymorphic cell layer, sometimes referred as to the hilus. It is the thinnest of the three dentate layers and contains the axons that cross from the granular layer to the cornu Ammonis.



Figure 2.12: Layers of the hippocampus. From [Duvernoy & Cattin, 2005].

2.5 Around the hippocampus

We give here a brief description of the surrounding anatomy of the hippocampus.

The nearest neighbour to the hippocampus is the amygdala. The amygdala is a structure mainly involved in emotional processes. The amygdala lies anteriorly and superiorly to the

hippocampus. The temporal horn of the lateral ventricle can sometimes be seen between the hippocampal head and the amygdala.

Anteriorly and inferiorly to the hippocampal head lies the parahippocampal gyrus. It includes the entorhinal cortex and also the perirhinal cortex. The parahippocampal region plays an important role in visual recognition, but there is also evidence that it makes a contribution to memory which can be distinguished from the contribution of the hippocampus [Eichenbaum et al., 2000]. Medially to the hippocampal head, the hippocampus borders the transverse fissure, in close proximity to the brainstem.

The lateral ventricles surround the hippocampal body by its lateral aspects. The parahippocampal gyrus runs parallel to the hippocampus along the base of its body.

Where the hippocampal tail becomes thinner, it is bordered laterally by the posterior lateral ventricle. The tail is adjacent to the posterior aspects of the thalamus, these two structures being separated by the lateral ventricle. The hippocampal tail finally joins the white matter bundle known as the fornix.

We now present a summary of the major intrahippocampal connections: the polysynaptic pathway and the direct pathway [Duvernoy & Cattin, 2005].

The first system, the so-called *polysynaptic pathway*, links all parts of the hippocampus by a long neuronal chain. The superficial layers of the entorhinal cortex provide the most prominent input to the hippocampus. Within the hippocampus, the flow of information forms a loop. The first step in the flow loop, known as the *perforant path*, is a set of fibers originating from the entorhinal cortex and projecting to the gyrus dentatus. Axons called mossy fibers, emerge from the dentate gyrus before entering CA3, and then CA2 and CA1 regions through the Schaeffer collaterals. Finally, the information is sent from the CA1 subfield to the subiculum (Figure 2.13).

We can identify another circuitry: the *direct pathway*, which directly reaches out the neurons of the hippocampus, without following the usual polysynaptic chain. The direct pathway finds its origin in layer III of the entorhinal cortex. From this layer, fibers directly reach the pyramidal neurons of CA1. CA1 neurons project onto the subiculum, the axons of which return to the deep layers of the entorhinal area (Figure 2.14).

2.6 Cognition

The hippocampus plays an important role in various cognitive processes. Their description is beyond the scope of this thesis. Here, we briefly review some of its key roles.

2.6.1 Hippocampus and memories

The patient HM Advances in research can sometimes occur in a surprising way. The importance of the hippocampus in the encoding and retrieval of memory processes has been recognized following the works of Scoville and Milner [Scoville & Milner, 1957]. Their primal goal was to study the effects of the surgical resection of medial temporal lobe for treatment of epilepsy. They describe for the first time in 1957 the case of a 29 year old man, the patient "H.M". This patient had one of the most severe cases of amnesia ever observed, his amnesia being the result of neurosurgery performed on him to treat the symptoms of his epilepsy.



Figure 2.13: Polysynaptic intrahippocampal pathway. A-E are parts of the neural chain forming this pathway. 1: alveus, 2: stratum pyramidale, 3: Schaffer collaterals, 4: axons of pyramidal neurons, 5: strata lacunosum and radiatum, 6: stratum moleculare, 7: vestigial hippocampal sulcus, 8: stratum moleculare, 9: stratum granulosum. From [Duvernoy & Cattin, 2005].

He has been followed for over 40 years by more than 100 researchers, and is the subject of dozens of research papers and book chapters. This man was a high school graduate, and had a IQ of 104 before his operation. After a bicycle accident in the age of nine, he began at the age of ten to suffer from frequent and moderate seizures. At sixteen, his seizures increased in power and intensity, despite the use of anticonvulsants. Surgery was decided upon and carried out on 1 September 1953: a removal of both medial temporal lobes was carried out, extending posteriorly for a distance of 8 cm (see figure 2.15). Two thirds of both hippocampi were removed. After the intervention, the authors mention that HM continues to suffer from seizures, but that "they were less disabling than before".

A psychological examination was conducted on 26 April 1955. The examinators noted that this patient was suffering from retrograde amnesia limited to a period of 11 years prior to his surgery at age 27. His memories formed before age 16 are still intact. In addition, it suffering from anterograde amnesia¹: although he can store new information temporarily in his short-term memory, he can no longer form any new long-term memories, and did not remember, for example, seeing the doctor a few minutes before. Psychological testing showed that his IQ was 112, (slightly better than before the operation), he presented no

¹Two other examples of anterograde amnesia : Dory from Nemo and the hero of the movie Memento, see figure2.16



Figure 2.14: Direct intrahippocampal pathway. The entorhinal area projects directly onto CA1 pyramidal neurons (1), which innervate the subiculum (2). Subicular axons project back to the deep layers of the entorhinal cortex (3). The neurons of these layers send axons to the association cortex (4). From [Duvernoy & Cattin, 2005].

disturbances of perception, abstract thinking, of reasoning skills or motivation. In summary, patient HM suffered only anterograde and retrograde amnesia but showed no disturbances of intelligence or personality. This amnesia apparently came from the absence of the temporal lobe. For the first time, an obvious link between memory and brain structure was revealed.

What tells HM about memory The experimental approach of the modern study of memory began with patient HM. Since 1953, he has been the involved in over one hundred experiments (for review see [Corkin, 2002]), using different paradigms. However, a study conducted by Milner in 1962 [Milner, 1962] remains indispensable for understanding the current view of the neurobiology of memory. In this study, the patient had to draw a complex figure without seeing directly his hand but with a mirror. This task requires to correct all his habits of visuomotor coordination. During testing, this patient has improved its performance in a manner similar to controls but has no memory of his previous trials, claiming to never have done this test. From this original experience, a conclusion can be made: there is a memory accessible to consciousness (the *declarative memory*) and a second type, a memory independent of the first, which deal with motor skills (the *non-declarative memory*). For the patient HM, only the first was impaired after the operation while the second was intact. The



Figure 2.15: Bilateral resection of the anterior temporal lobe in patient HM.



Figure 2.16: Anterograde amnesia in Hollywood : In *Memento*, Guy Pearce plays Leonard, who suffers severe anterograde amnesia after sustaining a head injury. Leonard retains his identity and the memories of events that occurred before the accident, but loses all ability to form new memories. In *Finding Nemo*, a reef fish called Dory, has a profound memory deficit which prevents her from learning or retaining any new information, remembering names, or knowing where she is going. As a result, she gets lost when left alone and is often found in a state of confusion.

modern notion that there are different types of memory was born.

Four points have to be retained about HM's case :

- Memory has a distinct neurobiological support: it is a function separable from other cognitive abilities, that one can quantify and experimentally study.
- The medial temporal lobe is not needed for short-term memory, since HM retained a number or a visual image for a short time. However these memories are not stored: it exibhits the difference between encoding and storage.
- Memory is not "stored" into the medial temporal lobe, since childhood memories of HM are intact.
• There is a dissociation between declarative and non-declarative memory (see below for more details).

Different types of memory Memory is the capacity of the nervous system to benefit from experience. It takes many forms, from simple to complex, from highly specific to most general. Any claim about "memory" or "memory impairment" immediately requires clarification: which kind of memory are we talking about?

As we have seen in the previous paragraph, we can identify at least two types of memories: an explicit (declarative) and an implicit (non-declarative) memory. The distinction between declarative and nondeclarative memory is fundamental, because it has turned out that different kinds of memory are supported by different brain systems.

Other memory system organizations have been proposed, they are briefly presented in the following.

■ *Short-term memory* Our memory is structured in several sub-systems, each comprising different categories of memories. A classic kind of categorisation is based on the amount of time the memory is stored: thus we can distinguish short-term memory, including working memory, from long-term memory.

Working memory refers to the capacity to maintain temporarily a limited amount of information in mind, which can then be used to support various cognitive tasks, including language comprehension, learning, reasoning, and preparation for action [Baddeley, 1992].

■ *Long term memory Long-term memory* keeps information lasting for several days or even years. It is divided into four different types of memory: episodic, semantic, procedural, and perceptual.

Episodic memory concerns events experienced personnally by the individual and their context (date, place, emotions). It gives the subject the impression of reliving the moment. This the autobiographical part of the episodic memory. It is also the registration of individual information in the specific context of occurrence.

Semantic memory is the general knowledge about the world and ourselves (our profession or our age). It stores the concepts of words and their meaning. Semantic memory is considered a network of associations between the word and concept, such as canary and bird. This memory is usually the most sustainable. It does not assume remembering specific events.

Procedural memory records the actions whose use becomes automatic over time (tying shoelaces, drive a car), elaborate mental procedures (protocol to solve a math problem, game strategies).

Perceptual memory retains the information provided by the senses of the shape of objects, texture, or smell. It is requested without the knowledge of the subject automatically. Perceptual memory comes into action before the percept has one meaning: in the context of visual perception, we perceive a form prior to identifying it.

In conclusion, we can note that the separation between these different types of memory is hard to do: autobiographical memory includes episodic elements, as well as semantic elements. In addition, these memories are complementary and interact.

2.6.2 Spatial navigation

The hippocampus also has a main role in spatial navigation functions, particularly in finding shortcuts and new routes between familiar places. A study at University College London focused on the hippocampus in taxi drivers [Maguire et al., 1998, 2000]. London's taxi drivers must learn a large number of places and the most direct routes between them (they have to pass a strict test before being licensed to drive). The study showed that the posterior hippocampus was larger in taxi drivers than in a control group. The anterior hippocampus, however, was larger in controls. In that study, the authors examined the correlation between these volume changes and time spent as a taxi driver. They found that the amount of time an individual worked as a taxi driver correlated positively and negatively respectively, with the volume of posterior and anterior portion of the hippocampus.

2.7 Implication in pathologies

Various clinical conditions are associated with alterations of the hippocampal formation. They may selectively affect different parts of hippocampus, each of the different hippocampal cytoarchitectonic fields being more or less vulnerable to damage. Conditions associated with hippocampal changes include, among others, dementia (Alzheimer's disease, fronto-temporal dementia ...), epilepsy and psychiatric disorders (depression, schizophrenia ...). Here, we briefly present its implication in Alzheimer's disease and temporal lobe epilepsy.

2.7.1 Alzheimer's disease

In 1907, Alois Alzheimer described for the first time the main neuropathologic characteristics of a disease which mainly caused impairment of memory, and disorientation followed by depression. Pathological examination revealed atrophy and specific brain lesions, localized in the cortical grey matter. The lesions of Alzheimer's disease (AD) are of two types: the *amyloid plaques* and the *neurofibrirally tangles* (NFT).

The progression of AD pathology is stereotyped. In [Braak & Braak, 1991], the progression is divided into six stages, based on the distribution of NFT: the lesions are first located in the trans-entorhinal cortex area (*stade I*), then spread into the entorhinal cortex (*stade II*), extend to the hippocampus and the limbic lobe(*stade III and IV*), involve the association neocortex (*stade V*) and finally the primary cortex (*stade VI*). These stages are divided into entorhinal (I and II), limbic (III and IV) and neocortical phases (V and VI), and are closely associated with clinical and cognitive deterioration, reflecting the degeneration of the cortical areas associated with these functions. The medial temporal lobe and the hippocampus are thus affected by NFT and neuronal loss at the earliest stages of the disease.

At present, the only way to obtain a definite diagnosis for AD is to perform an autopsy of the brain of probable AD sufferer, revealing the density and distribution of amyloid plaques and NFT. The diagnosis of probable AD relies on clinical criteria, based on neuropsychological examination. An important question for research is to make progress towards earlier and more accurate diagnosis of AD, by discovering markers of early AD. In particular, magnetic resonance imaging (MRI) allows visualizing brain atrophy which reflects neuronal loss. A vast amount of research has thus been carried out to extract diagnostic markers of AD from MRI.



Elderly healthy subject

Alzheimer T0

Alzheimer T0+2 years

Figure 2.17: Coronal slices of T1 weighted MRI, showing the atrophy of the hippocampus. The first panel comes from an elderly healthy subject. The two next panels show the hippocampal atrophy in an AD patient at T_0 and T_0 + 2 years. The hippocampi are marked with the white arrows.

Several volumetric MRI studies have highlighted increased atrophy of the hippocampus in the earliest stages of the disease [Laakso et al., 1995; Bobinski et al., 1999]. They showed that the volumetry of the hippocampal region is a reliable marker of the moderate to severe stages of the disease, with a sensitivity and specificity above 80% [Frisoni et al., 1999; Du et al., 2001]. However, at the stage of mild cognitive impairment (MCI), the sensitivity of hippocampal volumetry is much lower [Convit et al., 1997; Pennanen et al., 2004]. This may be because early pathology selectively affects some specific parts of the hippocampus, NFT and neuronal loss being dominant in CA1 and the subiculum [Hyman et al., 1984; Van Hoesen & B.T., 1990]. New imaging techniques and mathematical shape models that could measure local atrophy have thus the potential to provide more efficient diagnostic tools.

2.7.2 Epilepsy

Epilepsy is a brain disorder characterized by generalized or focal epileptic seizures. Among the different forms of focal epilepsies, temporal lobe epilepsy (TLE) is of special interest since this is the most common variant in adults accounting for about 40% of cases [Engel, 1996]. The association between hippocampal abnormalities and temporal lobe epilepsy is well documented in the literature. In particular, hippocampal sclerosis is a frequent finding in patients with TLE [Eriksson et al., 2008]. However, it is not yet clear whether the epilepsy is caused by hippocampal abnormalities, or whether the hippocampus is damaged by cumulative effects of seizures.

In about 70% of TLE patients, seizures cannot be controlled with medication. In carefully selected patients, epilepsy surgery can effectively control seizures [Wiebe et al., 2001]. MRI plays an important role in the pre-surgical evaluation by allowing the identification of atrophy or altered signal intensity in the hippocampus suggesting hippocampal sclerosis. When atrophy is found, more than 70% of surgically treated TLE patients achieve seizure freedom after surgery [Wiebe et al., 2001; Wiebe, 2003]. On the other hand, hippocampal volumes

are normal in about 20% of patients with electro-clinical signs of mesial TLE [Jackson et al., 1994]. In these "MRI-negative"TLE cases, the MRI is therefore unable to show a potential surgical target. In the absence of identifiable structural pathology on MRI, these patients currently undergo invasive EEG monitoring with intracranially implanted electrodes and have a lower chance of success after surgery than those in whom a lesion is found. It is thus important to design new MR image analysis approaches that could unveil subtle hippocampal abnormalities that cannot be detected by standard means.

2.8 In vivo visualization using MRI

Magnetic Resonance Imaging (MRI) is the imaging technique of first choice for visualization of the hippocampal structure due to the high contrast between different tissues (figure 2.18).



Figure 2.18: Vizualization of the hippocampal structure in conventional T1-weighted sequence. The hippocampus, marked with the arrows, can be seen in coronal (a), sagittal (b) and axial (c) planes.

It provides anatomical images of three-dimensional nature, composed of small volume elements (voxels). Creating images requires no anatomical tracer injection and no radiation exposure. MR signal is essentially produced by protons. Each proton rotates around its own axis. When a strong magnetic field and a radio frequency (RF) pulse are applied at angles orthogonal to each other, the protons as a group begin to precess about their own axis in synchrony with each other. When the RF pulse is turned off, the system returns to normal and in doing so create small local magnetic fields which in turn gives rise to small electric currents in receiving coils. It is this current that is ultimately measured in MRI.

Classically, at 1.5T or 3T, the hippocampus is visualized using 3D T1-weighted sequences with about 1mm isotropic resolution (figure 2.20). Using T1-weighted sequences, manual segmentation of the hippocampus can be performed using standardized protocols [Hasboun et al., 1996; Pruessner et al., 2000]. However, manual segmentation is very time consuming (over 1 hour per structure) and suffers from considerable intra and inter-rater variability. Automatic segmentation approaches have thus been proposed [Fischl et al., 2002; Coupé et al., 2011; Lötjönen et al., 2011]. In our laboratory, Marie Chupin has developed the automatic approach SACHA [Chupin et al., 2007, 2009b] that segments the hippocampus and the amygdala from MR images 2.19. The segmentation uses simultaneous region deformation constrained by anatomical landmarks and knowledge derived from probabilistic atlases.

This method was validated by comparison with manual segmentations in healthy subjects, patients with Alzheimer's disease, and patients with epilepsy. The validation showed a high accuracy of the segmentation, with a relative error in volume of approximately 8% compared to manual segmentation.



Figure 2.19: SACHA: Automatic segmentation of hippocampus and amygdala. Left panel: Illustration of the final result on a sagittal reconstruction and on 3D surface renderings corresponding to the automated segmentations of the hippocampus (red) and the amygdala(green). Right panel, top: patient with Alzheimer's disease (coronal and sagittal reconstructions, from left to right). Right panel, bottom: healthy elderly control (coronal and sagittal reconstructions, from left to right). From [Chupin et al., 2009b; Colliot et al., 2008].

However, conventional T1-weighted sequences allow only visualizing the external boundaries of the hippocampus and not its internal subparts such as the cornu Ammonis or the dentate gyrus. This is because:

- most of these substructures are too small to be correctly imaged with 1mm resolution;
- T1-weighted images display almost no contrast between them.

On the contrary, T2-weighted spin echo sequences provide contrast between some of these subfields. [Mueller et al., 2007] used T2-weighted sequences with 0.4x0.5x2mm resolution at 4T to measure the subiculum, CA1, CA2 and CA3/4 and the dentate gyrus with applications in epilepsy [Mueller et al., 2009] and Alzheimer's disease [Mueller & Weiner, 2009]. However, their approach involves the definition of many arbitrary landmarks. Moreover, using 2mm thick slices prevents from building 3-dimensional models of the subparts.

7T MRI provides new contrast and increased spatial resolution. At 7T, Chupin et al. [2009c] used T2-weighted spin echo sequences with $250\mu mx250\mu mx1mm$ resolution to segment CA, the dentate gyrus (together with CA4), the subiculum, the alveus and the fimbria. They further applied their approach to patients with temporal lobe epilepsy [Henry et al., 2011]. Wisse et al. [2012] also proposed manual segmentation of the hippocampal subfields at 7T. Kerchner et al. [2010] used 7T MRI to detect subregional atrophy of CA in Alzheimer's disease. However, they did not perform volumetry of the different subfields. In our laboratory, we are currently imaging patients with Alzheimer's disease, MCI and healthy controls at 7T. On a restricted subset of patients, Claire Boutet performed subfield volumetry and found marked atrophy in the left subiculum [Boutet, 2012].



Figure 2.20: Coronal, sagittal and axial MRI views of the hippocampus. A 3D structure is superposed to the scans for a better representation.



Figure 2.21: Coronal slice of 7T MRI, at the level of the hippocampal head. Contrary to conventional T1-MRI, we can clearly distinguish the Cornu ammonis and the gyrus dentatus. From [Chupin et al., 2009c]

2.9 Conclusion

In this chapter, we described the anatomy of the hippocampal formation, its different subparts and connections. We also briefly reviewed its role in cognition and in two disorders: Alzheimer's disease and epilepsy. Volumetric measurements of the hippocampus can prove useful to assist the diagnosis of Alzheimer's disease or for the presurgical evaluation of patients with temporal lobe epilepsy. However, these global measures cannot detect local alterations of the hippocampus and their diagnostic value is therefore limited. On the contrary, mathematical shape models have the potential to detect subtle abnormalities. In the next chapter, we will review existing approaches for shape analysis of brain structures.



SHAPE ANALYSIS

Advances in medical imaging technology have provided the ability to acquire high resolution 3D images of the human brain. In particular, magnetic resonance imaging (MRI) is a fantastic non-invasive mean for investigating human anatomy in-vivo and provides high resolution images whose utility is beyond the simple visual inspection. Quantitative study of anatomical shape and its variation is of high importance to understand the mechanisms and the impacts of diseases such as neurodegenerative or neurodevelopmental disorders. Many studies rely on the statistical analysis of volume measurements [Aylward et al., 1999; Colliot et al., 2008]. While they can detect volumetric changes between patients and healthy controls, they do not capture the complexity of a shape. Medical images can provide highly detailed shape information for analysis of morphological variability within a single population or among different groups of subjects.

Indeed, a quantitative shape analysis would be of special interest to understand morphological changes caused by neurological or psychiatric diseases like schizophrenia [Styner et al., 2004], autism [Dager et al., 2007], epilepsy [Hogan et al., 2004] or Alzheimer's disease [Apostolova et al., 2006a]. Brain anatomy is thought to change with the progression of these diseases. One motivation for shape analysis is its potential ability to provide relevant information which helps doctors providing a diagnosis. Beyond assisting the diagnosis, shape analysis can also offer a way to quantify the development of a disease or the effect of a treatment [Gerig et al., 2003], or investigate anatomical differences associated with age or gender [Bouix et al., 2005]. It is also important for a shape analysis method to not only demonstrate that there are shape differences, but also to identify where and how these differences occur. For example, recent evidence suggests that Alzheimer's disease affects the shape of some parts of the hippocampus more than the others [Apostolova et al., 2006a; Mueller & Weiner, 2009]. These results could allow to focus future research on these specific substructures.

Shape characterization can also aid understanding anatomical variability by providing statistical anatomical atlases. Currently, most anatomical atlases show a single instance of the normal anatomy of brain structures [Duvernoy & Cattin, 2005; Paxinos & Mai, 2004].

The estimation of the variability in the shape of a brain structure and the construction of an atlas that incorporates this variability can not only be useful from an educational point of view, but can also improve automatic image segmentation algorithms by imposing a prior on the shape of the objects being segmented or provide a basis to study the genetic and environmental determinants of anatomical variability.

This chapter provides an overview of the main shape modeling. First, we introduce the concept of shape. Then, we review four main categories of shape descriptors: contour-based, interior-based, deformation-based and thickness measurements.

3.1 What is a shape?

Shape is an ill-defined term, that can refer to the "the outward form of an object produced by its outline", "the particular physical form or appearance of something". These definitions are related to human visual perception. Although describing shape features or capturing shape differences of 3D objects seems not to raise difficulties for humans, the mechanism that makes this possible is unknown.

The representation and the analysis of objects is a challenging problem. No general shape description exists that solves all shape related tasks. Many disciplines such as computer vision or molecular biology developed specific shape descriptions adapted to a specific task. In the following, we limit our review to include only shape descriptors that have been used in medical image analysis.

Shape can be defined as the geometry of objects that is invariant under translation, rotation, and scaling [Kendall, 1984]. This definition of shape provides an equivalence relation between objects, that is, two objects have the same shape if one can be transformed into the other by only a translation, rotation, and uniform scaling (fig3.1). If we consider that the information given by the size is relevant, one can consider shape as the geometric information invariant by translation and rotation only.

The purpose of the following section is to provide a brief overview of existing descriptors.

3.2 Shape Descriptors

This section provides a summary of shape descriptors. A shape descriptor represents the object shape at a certain level of abstraction. Instead of representing the original shape as accurately as possible, a shape descriptor extracts the important features of the shape from the perspective of a specific application.

The simplest quantitative shape descriptors can be reduced to one value, such as volume, perimeter, or eccentricity of the shape. They are useful to compare shapes with large differences. However, for a fine representation of shapes, we need more sophisticated models. Good descriptors must satisfy desirable properties: they have to be invariant under rigid transformations. They also have to be discriminative enough, and assign different values to different shapes, while providing a robust estimation of the shape (small perturbations in the initial object should not lead to large changes in the descriptor). Depending on the



Figure 3.1: Three objects that have the same shape, with different positions, orientations, and scales.

problem, other properties may be required, such as efficiency (non-redundancy of the information), localization, or preservation of the information (in other words, the description fully characterizes the object, and an inverse transform is possible).

Image-based morphological studies typically consist the following five main steps.

First, any morphological study starts with data acquisition. One or more volumetric scans are acquired for each subject. In this work, we will work exclusively with MR images. Data acquisition, as well as recruitement of the subjects included in the study, is a relatively consuming task in medical imaging studies. This results sometimes in a relatively small sample size, and statistical interpretation of the results may be compromised. This a significant challenge, especially in case of the development of learning algorithms.

Then, the anatomical structures of interest are segmented, either manually or using an automatic algorithm designed for this task. Exemples of manual hippocampal segmentation methods can be found in [Hasboun et al., 1996; Pruessner et al., 2000]. These methods suffers from intra and inter-variability, and are relatively time-consuming. Automated methods have been proposed to overcome these disadvantages [Kelemen et al., 1999; Yang & Duncan, 2004; Duchesne et al., 2002; Fischl et al., 2002; Shen et al., 2002; Chupin et al., 2009b]. After this step, the shape is represented by elements that enumerate their interior, called volume elements or voxels. The structure of interest is described by a binary voxel shape. This is a geometric representation of the shape, that views the world as black and white: it distinguishes between interior and exterior voxels only, and does not take into account the intensity at each voxel.

The binary voxel shape is a low-level description of the object, that can be hardly used for a good understanding of the shape¹. Thus, the third step consists in defining an abstract

¹However, it is possible to use local concentration of gray matter instead of binary voxel shape. This method, known as voxel-based morphometry (VBM), involves spatially normalizing highresolution images from all the subjects in the study into the same stereotactic space. Then, this is followed by gray-matter segmentation of the spatially normalized images, smoothing of the gray-

representation of the shape that can characterize the structure. Quantitative measures are extracted from each input segmentation and combined into a representation that describes the shape. This representation can be for example a vector, a set of points or a graph, and must ideally be independent of the image acquisition or the modality considered. Various shape descriptors have been proposed, this section gives a brief summary of existing descriptors.

The fourth step is the normalization of the descriptors. This step covers two complementary issues: the invariance of the descriptors and the establishment of correspondances between the components of the descriptors, in order to perform comparisons and generate statistics. Many representations are not invariant under rigid transformations, which is typically solved by aligning all shapes, or bringing them in a "standard" pose. This alignment establishes implicit correspondences between the features inside the descriptor. We can distinguish two types of correspondences: the first class relies on coordinate-based appraoches, and consists on point-to-point matching; the second alternative searches for correspondences between objects [Trouvé, 1998; Vaillant & Glaunes, 2005; Miller, 2004]. The problem of finding correspondences across individuals is very difficult. A main obstacle is that it is unclear what a "true" correspondence between two instances of an anatomical structure is.

Then the set of (normalized) descriptors is used to construct either a generative model of shape variation [Allassonnière et al., 2007; Durrleman et al., 2011] or a discriminative model of shape differences between two populations [Styner et al., 2004; Csernansky et al., 2000]. Traditionally, a generative shape model is formed by a mean shape and a variability model. The mean shape is obtained after alignment of the population and optimally represents all observations. The variability model contains information about how much and in which way the mean shape can be deformed, while still representing a plausible anatomical structure. A large number of observations have to be evaluated to provide an accurate statistical shape model. The methods used for the computation of the mean shape as well as the variability model depend on the representation of the shapes.

3.2.1 Contour-based descriptors

3.2.1.1 Point distribution models

Point distribution models (PDM) may be the simplest way to give a local description of the object boundary. Shapes are represented by a discrete sampling of the object contours. Points of correspondence on each object that match between subjects are called landmarks. This approach to shape analysis has been mainly developped by Kendall [Kendall, 1984], Bookstein [Bookstein, 1991], or Dryden and Mardia [Dryden & Mardia, 1998].

Dryden defines three basic types of landmarks: anatomical, mathematical and pseudolandmarks.

• An anatomical landmark is a point assigned by an expert that corresponds between biological objects.

matter segments, and voxel-wise parametric statistical tests [Ashburner & Friston, 2000]

- Mathematical landmarks are points located on an object according to some mathematical property of the figure, (e.g. high curvature)
- Pseudo-landmarks are constructed points, located between the other two types of landmarks or points around the outline, or on a regular grid over the surface.

The shape analysis then works on landmark coordinates directly. This approach seems to be the most intuitive technique to describe a boundary, but it is limited in that automatic detection of landmarks is not straightforward and the shape analysis is very sensitive to the choice of landmarks. Moreover, a one-to-one correspondence must be established to compare individual shapes, which may be difficult and sometimes almost impossible to define for complex and variable shapes such as the human cortex. Moreover, these techniques only deal with collection of points and do not take into account geometric information of a higher level, such as normals or tangents of the structures.

In the Active Shape Model proposed by [Cootes et al., 1995], a number N of landmarks points are annotated on the contour of a set of training images, and each shape is represented by a vector of size 2N/3N. Shapes are rigidly aligned by procrustes alignment ². Principal Component analysis (PCA) on the aligned shapes gives a statistical model of the distribution of the landmarks position. This model is used for generating new objects, by varying parameters of the main modes, or to localize shapes in new instances by fitting the model.

Styner et al. [2006] introduced a PDM based on spherical harmonic (SPHARM) decomposition and spherical parameterization. A detailed presentation of this method will be provided in section 3.2.1.2.

3.2.1.2 Parameterization and surface expansion

In this dissertation, we focus on objects of spherical topology. For such objects, let (x, y, z) denotes cartesian object space coordinates and (θ, ϕ) polar parameter space coordinates. A parametric surface description defines the object surface as follows :

$$\nu(\theta,\phi) = \begin{pmatrix} x(\theta,\phi) \\ y(\theta,\phi) \\ z(\theta,\phi) \end{pmatrix}$$
(3.1)

Many applications define the fonction $v(\theta, \phi)$ as a linear combination of a collection of basis functions f_i . The set of functions can be finite or infinite (in which case a finite part of the series will be used for practical purposes). The individual coordinate functions take the following form :

$$(x(\theta,\phi), y(\theta,\phi), z(\theta,\phi)) = \left(\sum_{i} c_i^x f_i(\theta,\phi), \sum_{i} c_i^y f_i(\theta,\phi), \sum_{i} c_i^z f_i(\theta,\phi)\right)$$
(3.2)

If the set of basis functions is fixed, the shape of a given object with spherical topology can be determined by the finite set of coefficient c_i^x , c_i^y , c_i^z . Some parametric descriptors are

²An iterative procedure for the estimation of the best rigid transformation which minimizes the sum of square differences between an individual shape and the empirical mean

based on the decomposition of the object using a particular functional basis, such as Fourier Series or splines.

Unlike the statistical features derived from landmarks, features computed as coefficients of basis functions have global support: a local change to the geometrical form of an object can change the values of all of the features describing the object.

SPHARM decomposition The Spherical Harmonic (SPHARM) description is a hierarchical, global, multi-scale boundary description that can only represent objects of spherical topology. The basis functions of the parameterized surface are spherical harmonics. Spherical harmonics are the angular portions of the solution to Laplace's equation in spherical coordinates and form an orthonormal set of basis function on the sphere. Using a linear combination of these basis functions, any function on the sphere can be approximated up to a predefined accuracy. Truncating the spherical harmonic series at different degrees results in object representations at different levels of detail, as is shown in figure 3.2. SPHARM is a smooth, accurate fine-scale shape representation, given a sufficiently small approximation error. In the next paragraph, we briefly describe the mathematical properties of spherical harmonic descriptors.

Spherical Harmonic basis function Y_l^m , $-l \le m \le l$ of degree l and order m are defined on $(\theta, \phi) \in [0; \pi] \times [0; 2 * \pi)$ by the following definitions :

$$Y_l^m(\theta,\phi) = \sqrt{\frac{2l+1}{4\pi} \frac{(l-m)!}{(l+m)!}} P_l^m(\cos\theta) eim\phi$$

$$Y_l^{-m}(\theta,\phi) = (-1)^m Y_l^{m*}(\theta,\phi)$$

To express a surface using spherical harmonics, the three coordinate functions are decomposed and the surface $v(\theta, \phi) = (x(\theta, \phi); y(\theta, \phi); z(\theta, \phi))$ takes the form

$$\nu(\theta,\phi) = \sum_{l=0}^{\infty} \sum_{m=-l}^{l} c_l^m Y_l^m(\theta,\phi)$$
(3.3)

where the coefficients c_l^m are three-dimensional vectors due to the three coordinate functions.

by setting
$$Y_{\ell m} = \begin{cases} \frac{1}{\sqrt{2}} \left(Y_{\ell}^{m} + (-1)^{m} Y_{\ell}^{-m} \right) = \sqrt{2} N_{(\ell,m)} P_{\ell}^{m}(\cos\theta) \cos m\varphi & \text{if } m > 0 \\ Y_{\ell}^{0} & \text{if } m = 0 \\ \frac{1}{i\sqrt{2}} \left(Y_{\ell}^{-m} - (-1)^{m} Y_{\ell}^{m} \right) = \sqrt{2} N_{(\ell,m)} P_{\ell}^{-m}(\cos\theta) \sin m\varphi & \text{if } m < 0. \end{cases}$$

where $N_{(\ell,m)}$ denotes the normalization constant as a function of l and m .

By truncating the series up to the degree *L*, we obtain a surface description by a set of $3 * (L+1)^2$ coefficients. The coefficients of different degrees provides a measure of the spatial frequency components of the structure.

So far, the surface description still depends on translation, rotation and scaling of the original object. [Brechbuhler et al., 1995] proposed a method to overcome these dependancies. Translation invariance can be achieved by ignoring the first coefficient c_0^0 which adds a constant term to each coordinate *x*, *y* and *z*.



Figure 3.2: Spharm-PDM representation of an hippocampal surface. Using spherical harmonic basis functions, we obtain a hierarchical surface description that includes further details as more coefficients are considered. The series have been truncated to degrees 1, 5, 12 and 20.

Any three real-valued linear combinations of the first order harmonics Y_1^{-1}, Y_1^0, Y_1^1 interpreted as coordinates in the object space will always describe an ellipsoid. Rotation invariance is achieved by rotating this ellipsoid to a standard position and applying this rotation to the coefficient. Scaling invariance can be achieved by dividing all coefficients by the length of the longest main axis of the ellipsoid.

The SPHARM representation has been mainly used as a data reduction technique for compressing global shape features into small number of coefficients, and has been used to model various neuroanatomical structures such as ventricles [Gerig et al., 2001a], hippocampi [Shen et al., 2004; Styner et al., 2006] or amygdala [Shenton et al., 2002].

Chung et al. [2007] proposed to use the weighted-SPHARM description, a formulation that generalizes the traditional SPHARM by weighting each spherical harmonic basis such that the resulting representation becomes the solution of an isotropic diffusion equation on a unit sphere.

The discrete coordinate functions are parameterized by the weighted-SPHARM representation :

$$\nu(\theta,\phi) = \sum_{l=0}^{\infty} \sum_{m=-l}^{l} e^{-tl(l+1)} c_l^m Y_l^m(\theta,\phi)$$
(3.4)

The weighted-SPHARM encompasses the traditional SPHARM as a special case when t = 0. The weighted-SPHARM penalizes high degree spherical harmonics more than the classical SPHARM does, and can be used to reduce the Gibbs phenomenon traditionnaly observed with the Fourier or Spherical harmonic descriptors.

This method was applied in quantifying the amount of gray matter in a group of high functioning autistic subjects, or modeling amygdala shape variations in autism [Chung et al., 2008].

Wavelet decomposition Wavelets are an other set of basis functions on the sphere. In contrast to SPHARM functions, spherical wavelets (Sphwave) basis functions have local support at various scales. The basis is made of scaling functions (for example, hat function) defined at a coarse level and wavelets functions defined at finer scales. At a given scale j, wavelets functions are a combination of scale j and j + 1 scaling functions. The support of the functions decreases as the scale increases.

A function f on the sphere can be expressed as a linear combination of the coarsest scaling function and all the wavelet functions (up to a scale J) and coefficients :

$$f(x) = \sum_{k} \lambda_{0,k} \phi_{0,k}(x) + \sum_{j < =J} \sum_{k} \gamma_{j,k} \psi_{j,k}(x)$$
(3.5)

where

- $\lambda_{0,k}$ is a scaling coefficient, representing the low pass content of f.
- $\phi_{0,k}$ is the scaling function at scale *j* and location *k* (indication where on the sphere the function is centered).
- $\gamma_{j,k}$ is a wavelet coefficient at scale *j* and location *k*, representing localized variation of the signal *f*, at a frequency defined by the scale *j*.
- $\psi_{i,k}$ is the associated wavelet function.

Each shape could be described by a vector of Spherical wavelets coefficients. Spherical wavelets coefficients are both local and global descriptors, and accurately encode shape variations at multiple scales in a compact manner. This method requires a surface parameterization on a regular grid. Nain et al. [2007] used this description to learn a shape prior, in order to constrain a segmentation process (caudate nucleus and hippocampus). Yu et al. [2007] studied the patterns of cortical shape variation in newborns using Spherical wavelets description and Principal Component Analysis of wavelets coefficients.

3.2.1.3 Local measurement on the surface

The methods presented in this section use a mesh-based representation of the object, and compute in each vertex a value representing a characteristic property of the shape. This measurement can be local or global, and may help the definition of correspondances between different instances of structures. A difficulty is to define a measure which is relatively robust against the sampling of the surface.



Figure 3.3: a: An illustration of the ISC feature of an hippocampus. The ISC feature of six points (labeled as red dots) on the surface are plotted. b: The entropy of the ISC feature at each point is plotted on the surface, resulting to an entropy map. c: The surface is partitioned into five regions, based on the values of the entropy map. From [Shi et al., 2007]



Figure 3.4: The attribute vector in two dimensions: the area of a triangle formed by three points P_{i-n} , P_i , and P_{i+n} , is used as the n-th element of the attribute vector.

Shape context Intrinsic shape context (ISC), introduced in [Shi et al., 2007], is a geometric feature used to capture global characteristics of shapes. This method attributes to each point on the surface a measure reflecting its relative position to the other points. For each point p, a partition of the surface in bins is created, based on the geodesic distance to p. The ISC feature at point p is defined as the histogram of the areas of bins. This feature is based on the intrinsic geometry of shape, thus it is invariant to rotation and translation. It is also scale invariant. ISC moves continuously along the surface and different parts of the shape (head, body and tail for the hippocampus) show distinctive patterns. A global partition of the shape can be computed, based on the value of the entropy of the histogram at each point. Shi et al. [2007] used this method to automatically detect curve landmarks, and guide the mapping between hippocampal surfaces. This surface mapping algorithm was also used in [Leporé et al., 2009] to examine local size and shape differences in the hippocampus of blind and sighted subjects.

Attribute vectors Shen et al. [2001] proposed a method to characterize the geometric structure in a large neighborhood around each point of the surface. The shape is described

by a set of vectors, called attribute vectors. Each vertex is associated with a set of values, integrating the geometric structure around the vertex from a local to a global scale (figure 3.4), as well as statistical information. This representation is associated with an adaptative deformable model, which initially focuses on the most reliable parts of the shape. The proposed techniques have been used to segment brain structures and simultaneously define point correpondences between these structures (determined via similarity of attribute vectors).

3.2.2 Interior-based descriptors

3.2.2.1 Global shape descriptors

Geometric quantities such as volume, can be used as global shape descriptors. They are very compact descriptors but their use is limited because of their relative inaccuracy and their poor discriminative power. Much sophisticated models have been proposed, such as moments invariants or spectral decomposition.

Moments Moments are used in probability to briefly describe the distribution of a random variable. When applied to 3D binary images, they describe the shape distribution with respect to its axes. First moments capture both global and local geometric information about the shape, as its volume, the coordinates of the center of mass... A small set of global descriptors that are invariant with respect to translation, rotation and scale can be defined, the so-called moment invariants. Considering moment invariants up to order 3, one can describe the shape of an object by a set of 12 values, which embed simple shape information, such as bending, tapering, pinching. They require no pre-processing as they can be computed directly from binary images and impose no constraint on the object topology. However, interpretation of global shape descriptors like 3D invariants is a difficult task.

Moment invariants have been applied to the morphometry of cortical sulci. Mangin et al. [2004] advocate their use as an appropriate tool to detect population-dependent patterns of the cortical shape. Shape characterization by moment invariants is coupled to a clustering method in [Sun et al., 2007] to automatically infer stable patterns of the cortical sulci.

Laplace Beltrami spectrum Niethammer et al. [2007] described a methodology for global shape comparison based on the Laplace-Beltrami (LB) spectrum. Contrary to the approaches proposed in [Styner et al., 2006] or [Nain et al., 2007], which were restricted to surfaces with spherical topology, this method is applicable to any Riemannian manifold (a differentiable manifold with a distance). Moreover it requires no registration and depends only on the intrinsic geometry of the object. Extraction of a surface from a segmented binary volume is the only preprocessing step required.

The Laplace-Beltrami operator is the generalization of the Laplacian to Riemannian manifolds, and is defined as the divergence of the gradient. The LB spectrum is the family of the eigenvalues of the LB operator. The spectrum is an isometric invariant, as the divergence and the gradient depend only on the intrinsic geometry of the object. Moreover, by normalizing eigenvalues, objects can be compared independently of their position and scale. Statistical analyses of the surface-based LB spectrum could indicate the existence of shape differences between populations. Reuter et al. [2007] extended this methodology to the analysis of the volumetric LB spectrum . It could be computed directly from 3D binary image. Dirichlet and Neumann boundary condition are tested. Neumann spectra can detect statistically significant differences of two populations of shapes (here, caudate nuclei in patients with schizophrenia and controls). However, it should be noted that some non-isometric shapes could have the same LB spectrum, thus it doesn't characterize completely the shape. ³ Reuter et al. [2009] used topological features from eigenvalues as shape descriptors. For example, length of level sets of the first eigenfunctions is used as a measure of circumference of caudate head and tail.

3.2.2.2 Distance transforms

The distance transform generates a map whose value in each point of the object is the smallest distance from that point to the boundary of the object. The boundary is modeled implicitly as a zero level-set of the distance transform. A signed variant of the distance transform eliminates the singularity at the boundary. Distance transform is a piece-wise continuous function, whose singularity ridges form the object skeleton. Different metrics can be used, resulting in different types of maps.

Euclidian signed distance transform Golland et al. [2005] used Euclidian signed distance transform to extract features from shapes. Moments of the distance transform are used to align the shapes. Thus, interior points have more weight than boundary points in the alignment procedure. That guarantees stability to boundary irregularities. The step of statistical analysis is the main innovation of this paper. Indeed, after alignment, individual distance transforms are used as feature vectors to construct a classifier for distinguishing between two groups. Shape differences are captured by the classifier function and expressed as deformations of the original shapes. This introduces the concept of discriminative direction, which explicitly tells how to change any input of one given class to make it look more like an example from the other class without introducing any irrelevant changes.

Thompson et al. [2004] developed a method to map radial atrophy on hippocampal and ventricular surfaces. A medial curve is defined by relying the centroid of the boundary in each section (along the main axis of the structure). The radial distance between each point on the boundary and this medial core is mapped on each individual's surface. Distance fields indexing local expansions or contraction in surface morphology are statistically compared between groups, or in a longitudianl study. Although the radial distance to the medial core is intrinsic to the surface (invariant under rotations and translation), this method requires to compute a medial core, which depends on the position of the planar sections and thus of the orientation of the acquisition. It also requires to establish correspondences between points in surfaces. Apostolova et al. [2006a,b] used radial atrophy maps as features to predict

³This problem was previously adressed by Kac [1966] in this article wittily titled "Can One Hear the Shape of a Drum?"Indeed the frequencies at which a drumhead can vibrate depend on its shape. These frequencies are the eigenvalues of the Laplacian in the region. The central question is: from the knowledge of the frequencies, can we infer the shape ? A negative response was given some years later by [Gordon et al., 1992]

conversion of MCI to AD, and to find patterns of atrophy in MCI patients, compared to AD patients.

Poisson equation Poisson Transform (PT) assigns to each point in the interior of the object a value reflecting the mean time required for a random walk beginning at this point to hit the boundaries. This function is the solution of Poisson equation, with boundary conditions determined by points of the contour. The values assigned by the PT take into account many points on the boundaries, contrary to the distance transform which considers only the nearest points. Thus, PT is less sensitive to small perturbations on the contours. Use of PT for shape description first appears in [Gorelick et al., 2006], and was then used in the study of schizotypal personality disorder and brain of premature infants [Haidar et al., 2006], or as a shape prior for segmentation [Vesom et al., 2008].

3.2.2.3 Skeletons

Skeletons are geometric shape descriptors that are of a lower dimensionality than the shape they describe. They are centered within the shape and capture the topology of the shape in a compact manner.

Medial axis Transform The Medial Axis Transform (MAT) was introduced by Blum [1967]. The medial axis, or skeleton is the set of the centers of the maximal inscribed balls in an object. The medial axis transform is the set of the pairs consisting of the center and the radius of the spheres. An illustrative definition of the skeleton is given by the prairie-fire analogy. A fire is initiated simultaneously over the whole boundary of an object. This fire will propagate to the center, the skeleton is the loci where the fire fronts meet and extinguish themselves. The skeleton of the object is defined as the connected collection of these quench points. The object can be fully reconstructed from the MAT, since the distance to the original boundary is known in every skeletal point. The term "medial axis" does not refer to a straight line. In 3D we could replace this term by medial surface. The above definition gives a simple description of the medial axis, but its computation is quite sensitive to small boundary perturbations. Hence, many methods were developed not to find the precise skeleton of a discretized object, but rather to compute an approximation of the medial axis, robust with respect to noise in the boundary and to discretization.

Medial Representations M-Rep are based on the notion of medial atom. The definition given in [Fletcher et al., 2004] of a medial atom $m = (x, r, n_0, n_1)$ is a 4-tuple in $R^3 \times R + \times S^2 \times S^2$. *x* and *r* are respectively the position and radius of a maximal inscribed ball, and n_0 and n_1 are two unit vectors. They represent the tangency points of the inscribed ball with the boundary (see figure 3.5).

Medial atoms are connected to form a graph. The atoms grouped into a medial sheet approximate the medial surface, but have a simplified topology (no branchings). Indeed, small perturbations on the boundary could yield medial surfaces with different topologies for similar objects. M-reps overcome this problem by imposing a fixed topology to the medial models. A compromise must be found between the robustness of the description and the



Figure 3.5: Representation of a 3D medial atom and the portions of the implied boundaries associated with them. A medial atom as is defined by its position (x), radius(r), and two spoke directions (n_0 and n_1). From [Fletcher, 2004]

complexity of the represented objects. The M-rep is a multi-scale shape description. Indeed, increasing the number of atoms in the medial sheet results in coarse-to-fine description. The implied boundary of an M-rep figure is interpolated from the boundary points and corresponding normals implied by the medial atoms. Moreover, M-rep description permits an analysis both for thickness and position, contrary to surface-based methods, and describes the shape in a more intuitive manner. In [Styner et al., 2004], a M-rep model is previously computed, and individual M-rep descriptions are then fitted on the model. This step ensures one-to-one correspondence between medial atoms of different subjects. M-rep are based on SPHARM-PDM description, and Voronoi diagram is used for skeletonization. This method is used to analyse brain ventricles and hippocampi in schizophrenic patients. In [Yushkevich et al., 2003, 2006; Yushkevich, 2009], a continuous extension of M-reps, called CM-rep is introduced. A shape-based coordinate over the interior of the structure could also be defined with this model.

Reeb Graph A reeb graph of a scalar function defined on a surface is a graph whose nodes are centroid of the contours defined by the level sets of the function. To be a consistent shape descriptor, Reeb Graphs must be constructed from a function intrinsically defined on the surface (invariant by rigid transformations) and robust to noise on the boundary, to ensure regularity of the underlying graph. Shi et al. [2008] introduced an anisotropic Laplace-Beltrami on surfaces and uses the first eigenfunction of this operator for computation of Reeb

Graphs of cyngulate gyri. This eigenfunction is a smooth function, robust to irregularities on the surface, and its Reeb Graph is a good approximation of the skeleton.

3.2.3 Deformation-based descriptors

In this section, we present method that adopt a quite radically different point of view: instead of characterizing the shapes themselves, they aim at characterizing their differences, by studying the deformation that map shapes onto each other. These methods follow the ideas of D'Arcy Thompson [D'arcy Thompson, 1917]. In his pioneering work 'On Growth and Form', he attempted to explain biological patterns by means of mathematical principles. In particular, he argued that transformations of coordinates of corresponding points of different organisms could explain the similarities of their structures. The pattern theory developped by Grenander casted into a precise mathematical form Thompson's vision on biological variability. Computational anatomy was born.



Figure 3.6: Theory of transformations according to D'Arcy Thompson. From [D'arcy Thompson, 1917]

Descriptors in this class are based on non-rigid matching of an individual object to a template or of one individual to another. The "quantity" of deformation needed to warp one object to another defines a distance between shapes. This framework has the advantage to be compatible with many types of representations, from simple models such as points [Glaunes et al., 2004] or surfaces [Vaillant & Glaunes, 2005], to more complicated objects such as fiber bundles [Durrleman et al., 2011]. Assuming that changes in anatomical brain structures are constrained by physical properties, such as rules of elastic deformations or rules of fluid dynamics, a set of methods have been proposed to characterize anatomical shape changes. These methods derive statistical features from deformation fields that optimally warp each individual structure (described for instance by a set of points sampled from exteriors of objects) to a template structure (or vice-versa). Constrained registration results in a transformation vector field describing three-dimensional displacement, which

encodes local compression or expansion. Inter-subject comparisons are made by comparing the individual transformations.

3.2.3.1 Large Deformation High Dimensional Brain Mapping (HDBM-LD)

[Csernansky et al., 1998] studied hippocampal abnormalities in schizophrenia by analyzing transformation fields between individual shapes and a template. In each MR Scan (template + target) landmarks were placed manually by experts along the surface of each hippocampus and at external brain boundaries. Targets were aligned with the template by a coarse transformation, guided by the landmarks. A second fluid transformation was then applied. Combined with the coarse map from the first step, this yields a diffeomorphic transformation. Individual anatomy was described by the vector displacements in the surface of the hippocampal template. PCA reduces the dimension of the vector fields. Template anatomies (MR image volume, structure segmentation, or structure surface) are then mapped onto the targets through these transformations via trilinear interpolation. HDBM-LD can also be used to quantify the asymmetries of paired subcortical structures. The intrasubject transformations from one side of the brain to the other are examined, and variation away from zero becomes the measure of asymmetry [Wang et al., 2001]. Eventually, HDBM-LD can be used for quantifying changes in neuroanatomical shapes over time. For this purpose, the intrasubject transformations from the first to the second time point are examined, and variation away from zero again becomes the measure of change [Wang et al., 2003].

3.2.3.2 Large Deformation Diffeomorphic Metric Mapping (LDDMM)

In this framework, shapes are the orbit under a group of diffeomorphic transformations of a template. The group of diffeomorphisms is generated by integration of a vector field. As infinite dimensional diffeomorphisms can't be added (there is no vector space structure on this space), a metric structure must be defined on the group of diffeomorphisms. The metric distance in the group of diffeomorphism is the length of the geodesic connecting them. Given this metric, distance between shapes is defined by the distance between transformations that generated them.

These ideas are at the basis of the Large Deformation Diffeomorphic Metric Mapping framework (LDDMM) Trouvé [1998]; Dupuis et al. [1998]. This framework is particularly attractive for brain morphometry since it provides smooth and invertible deformations which are more likely to be consistent with the underlying anatomy. The mathematical foundation [Younes, 2010] ensures that optimization procedures find diffeomorphic optima and allows statistics to be performed on the results of registrations [Joshi et al., 2004].

More recently, LDDMM has been extended to the matching of current [Glaunes, 2005; Durrleman et al., 2009]. Currents provide a unified mathematical description of any sets of points, curves, surfaces or volumes. Currents model geometrical objects via their action on a test space of vector fields. The modeling based on currents consider objects as a mass distribution without any kind of parameterization. An important advantage of using currents is that they do not require to find homologous points across subjects, which is an ill-defined

problem. Currents also present the advantage to be robust to the change of connectivity of the structure, and to be less sensitive to the sampling of shapes than other methods.



Figure 3.7: In the framework of currents, curves and surfaces are tested on vector fields along the curves (left) or through the surface (right). From [Durrleman, 2010]

3.2.4 Thickness measurements

The estimation of cortical thickness from MRI data is an important topic in brain imaging. Thickness computation is particularly relevant for the cortex since it presents as a convoluted sheet. Cortical thickness analysis allows to relate cognitive abilities, effects of aging, and effects of diseases to structural changes in the brain. Changes in the thickness of the cortex are thought to reflect a change in the underlying cortical columns, such as neuronal loss or neuropil shrinkage.

Studies have suggested that various diseases such as Alzheimer's disease [Lerch et al., 2005] or psychiatric disorders [Shaw et al., 2006; Narr et al., 2005], may affect cortical thickness. Conversely, it has been shown that mental exercise such as meditation could result in increasing cortical thicknees in regions involved in attention and sensory processing [Lazar et al., 2005]. However, defining cortical thickness is a non-trivial task.

Cortical thickness is a distance metric between the boundaries of the white matter and the gray matter (inner boundary) and gray matter and cerebro-spinal fluid (outer boundary), but there are multiple ways of defining corresponding points on these two boundaries. Manual delineation of cortical thickness from MRI or post-mortem samples is very difficult, due to the necessity of creating a correct slice plane perpendicular to the cortical surface. Therefore, automatic measurements based on MRI data have been proposed. These approaches can be categorized into surface and volume based methods. The first step of surface-based methods is to extract inner (WM/GM) and outer (GM/CSF) surfaces from the volumetric data. Then, surface-based methods compute the length of the path connecting each point on the inner surface to a point on the outer surface. This path could be a straight line based on the minimum Euclidian distance, or constrained to follow the normal direction at the surface.

The straight line approach has some major drawbacks.

- Thickness is defined only at the surface and not throughout the mantle.
- Thickness measurements will vary depending on which surface you measure from.
- Lines of thickness can intersect.

3.2.4.1 Volume-based methods

Volume-based methods make the assumption that it is useful to assign a thickness value to each voxel inside the cortical mantle. Moreover, these methods do not need the extraction of inner and outer surfaces, which is a time-consuming step.

Methods based on Laplace's equation Laplace methods solve Laplace's equation for the potential between the inner and outer surface, thereby providing a more elaborated point correspondence between both surfaces.

Laplace's equation is a partial differential equation, which is used in the fields of electromagnetism and fluid dynamics. In 3-D, the problem is to find twice-differentiable real-valued functions (ϕ) such that :

$$\nabla^2 \phi = \frac{\partial \phi}{\partial x} + \frac{\partial \phi}{\partial y} + \frac{\partial \phi}{\partial z} = 0$$
(3.6)

For cortical thickness measures, each surface is assigned a potential (intensity) value. A solution of Laplace's equation then results in a smooth transition of voltages (intensities) from one surface to the other. From the obtained smooth field, a gradient value is calculated at each point of the cortical mantle. Integrating along these gradient values results in field lines or streamlines. Cortical thickness value at a boundary point is given by the length of the streamline connecting this point to the opposite surface. This mathematical model has been argued to give an anatomically plausible thickness measure, it assigns to each point of the surfaces a unique curve (flow line) that measures the thickness.

This framework was implemented in [Jones et al., 2000; Yezzi Jr & Prince, 2003] and extended in [Hutton et al., 2008] to identify regions of buried cortex and ensure that the thickness of grey matter within sulci is not over-estimated.

Unfolding Zeineh et al. [2001] applied a cortical unfolding method, firstly developed for the study of visual cortex, to provide activation maps of the hippocampal region . White matter (WM), gray matter (GM) and cerebro-spinal fluid (CSF) are first segmented within the medial temporal lobe. Then the volume inside the medial temporal lobe defined as GM is extracted and stretched until it is a two-dimensional surface, while maintaining topology and minimizing distance errors (without any cuts). A map of the different subregions (defined on 3D data) is projected on individual flat surfaces. This flattening procedure offers a better visualization of activation patterns in fMRI studies. However, the comparison of data across subjects requires alignment of flat surfaces into the same space. The first step of this alignment is to create an average template. Anatomical boundaries (figure 3.8) are averaged over all of the subjects and defines the template. Each subject is then warped on this template. The second step is to project the functional data onto the warped flat surface. Statistical

analysis is performed in flat space and provides activation maps onto the common space. This technique is employed in [Burggren et al., 2008] to measure cortical thickness reduction on the MTL among a population of APOE 4 carriers. Cortical flat maps are computed and thickness is estimated in the 3D space : for each voxel, in GM, the distance to the closest non-GM voxel is computed. The maximum value of the voxels corresponding to a pixel in flat map space is projected (and multiplied by 2), resulting in cortical thickness flat maps. For each region defined in the hippocampal region, a weighted mean thickness is computed (according to the area of the region in each hemisphere), and this value is used in statistical analysis. (No flat maps registration) Improvements to this method are presented in [Ekstrom et al., 2009]. The hippocampal formation is delineated from high resolution T2 weighted images and then interpolated along the z-axis to produce isotropic voxels. GM strip is flattened, hippocampal regions boundaries are delimited and cortical thickness is computed.



Figure 3.8: Steps of the unfolding method. A: White matter (grey), gray matter (green) and CSF (yellow) are defined within the medial temporal lobe. B: Regional boundaries are shown in color. C) Thickness map superimposed on the anatomical image. D) An averaged cortical thickness map in flat map space for the left hippocampus. Gray scale intensity represents cortical thickness. The boundary lines are color-coded to match the corresponding line from panel B. From [Burggren et al., 2008]

3.2.4.2 Surface-based methods

Surface-based techniques typically involve the generation of a triangulated mesh based on the WM boundary [Fischl & Dale, 2000; Fischl et al., 1999a], which is then deformed to find the opposite boundary.

Alternatively, WM and pial boundaries are defined, and simultaneously deformed [Mac-Donald et al., 2000]. Distance constraints ensure a realistic coupling of the two surfaces. The thickness of the cortex is then defined at surface points or vertices and is given by some measure of the distance between them.

One of the most used methods for estimating cortical thickness is implemented in the freely available FreeSurfer program.

3.3 Conclusion

Various approaches to shape analysis have been proposed in the medical imaging community and applied to the analysis of brain structures. There is currently no consensus on the methods of choice. The choice of a shape representation depends on the structure considered as well as the demands of the application.

In the two following parts of this thesis, we were driven by two distinct problems.

In Part II, our aim was to design a classification method based on hippocampal shape descriptors that could discriminate between patients and control subjects, and not to define new descriptors. Since the main motivation was classification rather than localization of changes, we chose spherical harmonics which provide a compact multiscale representation. Furthermore, spherical harmonics representation can be subsequently transformed into point-distribution models to localize differences.

In Part III, our aim was to design shape models of the hippocampal substructure which can now be imaged with the emergence of new acquisition techniques using 7T MRI. Since this substructure presents as a rolled-up gray matter ribbon, a thickness-based approach was a natural choice. However, approaches designed specifically for the cortex do not seem adapted to hippocampal substructure. We thus proposed a new variational approach based on Reproducing Kernel Hilbert Spaces (RKHS), which has the further advantage of producing a diffeomorphic flow. This approach was integrated within the Large Deformation Diffeomorphic Metric Mapping (LDDMM) for inter-individual comparison of thickness maps.

PART 2

STANDARD MRI



AUTOMATIC CLASSIFICATION OF PATIENTS WITH ALZHEIMER'S DISEASE BASED ON HIPPOCAMPAL SHAPE FEATURES

In this chapter, we propose a new method for the automatic classification of patients with Alzheimer's disease or mild cognitive impairment and elderly controls, based on hippocampal shape features. This approach can be applied to hippocampal segmentations performed on conventional MRI at 1.5T or 3T. The method was published in the following paper which is reproduced below:

E. Gerardin, G. Chételat, M. Chupin, R. Cuingnet, B. Desgranges, H.-S. Kim, M. Niethammer, B. Dubois, L. Garnero, S. Lehéricy, F. Eustache, O. Colliot, The ADNI, Multidimensional classification of hippocampal shape features discriminates Alzheimer's disease and mild cognitive impairment from normal aging, *NeuroImage*, 47 (4), 1476-86, 2009.

4.1 Abstract

We describe a new method to automatically discriminate between patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) and elderly controls, based on multidimensional classification of hippocampal shape features. This approach uses spherical harmonics (SPHARM) coefficients to model the shape of the hippocampi, which are segmented from magnetic resonance images (MRI) using a fully automatic method that we previously developed. SPHARM coefficients are used as features in a classification procedure based on support vector machines (SVM). The most relevant features for classification are selected using a bagging strategy.

We evaluate the accuracy of our method in a group of 23 patients with AD (10 males, 13 females, age \pm standard-deviation (SD)=73 \pm 6 years, mini-mental score (MMS)=24.4 \pm 2.8), 23 patients with amnestic MCI (10 males, 13 females, age \pm SD=74 \pm 8 years, MMS=27.3 \pm 1.4) and 25 elderly healthy controls (13 males, 12 females, age \pm SD=64 \pm 8 years), using leave-

one-out cross-validation. For AD vs controls, we obtain a correct classification rate of 94%, a sensitivity of 96%, and a specificity of 92%. For MCI vs controls, we obtain a classification rate of 83%, a sensitivity of 83%, and a specificity of 84%. This accuracy is superior to that of hippocampal volumetry and is comparable to recently published SVM-based whole-brain classification methods, which relied on a different strategy. This new method may become a useful tool to assist in the diagnosis of Alzheimer's disease.

4.2 Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia in the elderly and the number of affected patients is expected to double in the next 20 years [Ferri et al., 2005]. Accurate diagnosis of AD can be challenging, in particular at the earlier stage. Early diagnosis of AD patients is important because it allows early treatment with cholinesterase inhibitors, which have been shown to delay institutionalization, improve or stabilize cognition and behavioural symptoms [Ritchie et al., 2004; Whitehead et al., 2004]. In the past years, the early clinical signs of AD have been extensively investigated, leading to the concept of amnestic Mild Cognitive Impairment (MCI) [Dubois & Albert, 2004; Dubois et al., 2007; Petersen, 2004; Petersen et al., 2001; Winblad et al., 2004]. MCI patients have cognitive deficits but are capable of independent living. MCI may be symptomatic of a transition to early Alzheimer's disease. Until recently, the role of neuroimaging in the diagnosis of AD was mainly confined to ruling out other causes of dementia. Progress in image acquisition and analysis techniques has modified this perspective: the challenge for modern neuroimaging is to help in the diagnosis of early AD and particularly in amnestic MCI patients or prodromal AD [Dubois et al., 2007]. Three-dimensional (3D) magnetic resonance imaging (MRI) with high spatial resolution allows visualization of subtle anatomical changes and thus can help in the detection of brain atrophy at the beginning of the disease. Histopathological studies have shown that the hippocampus is affected by neurofibrillary tangles and amyloid plaques in the earliest stages of AD [Braak & Braak, 1995; Delacourte et al., 1999]. Many studies have thus used MRI to assess in vivo hippocampal atrophy in AD, using manual segmentation [Fox et al., 1996; Jack et al., 1992, 1998; Jack Jr et al., 1997; Juottonen et al., 1999; Killiany et al., 2002; Laakso et al., 1998, 1996; Lehericy et al., 1994; Seab et al., 1988; Xu et al., 2000]. These studies have demonstrated that hippocampal volumetry is a valuable marker of AD and can distinguish patients with AD from elderly controls with a high degree of accuracy (80% to 90%). However, in patients with MCI, the discriminative power of hippocampal volumetry is substantially lower (with reported accuracy ranging from 60% to 74%) [Convit et al., 1997; De Santi et al., 2001; Du et al., 2001; Pennanen et al., 2004; Xu et al., 2000]. Moreover, manual segmentation of the hippocampus requires a high degree of anatomical training, is observer-dependent and time-consuming (more than 1 h). We previously developed a fully automatic method to segment the hippocampus on MRI [Chupin et al., 2007, 2009b]. This method has been compared to manual segmentation in young healthy participants and patients with AD and has proved to be reliable, fast and accurate (about 8% relative volume error when compared to manual segmentation). We have evaluated the accuracy of automatic hippocampal volumetry to distinguish between patients with AD, MCI and elderly controls and found that it is similar to that of manual volumetry (84% for AD vs controls

discrimination, 73% for MCI vs controls) [Chupin et al., 2008; Colliot et al., 2008]. However, volumetric analysis only assesses global changes of the hippocampus. On the other hand, shape analysis methods can unveil local atrophy of the hippocampus and may thus be more sensitive than volumetry, in particular at the MCI stage. Radial mapping has been used to assess local atrophy of the hippocampus in AD and MCI [Apostolova et al., 2006a,b; Frisoni et al., 2006]. In concordance with histopathological studies, marked atrophy was found in a region corresponding to the CA1 subfield of the hippocampal formation and the subiculum [Frisoni et al., 2006]. Other studies relying on the high-dimensional brain mapping (HDBM) method [Csernansky et al., 2000; Wang et al., 2006] and a voxel-based approach [Chételat et al., 2008] also found a predominant atrophy in CA1. However, except for [Csernansky et al., 2000; Wang et al., 2006], these studies were restricted to group analysis and, in their present form, most of these methods cannot be used to classify individual patients. [Csernansky et al., 2000] used the HDBM approach to classify patients with very mild AD and controls. However, they did not investigate the classification of MCI patients and it remains unclear whether the diagnostic accuracy of this approach is superior to that of volumetry. Recently, there has been a growing interest in the use of multidimensional classification methods, such as support vector machines (SVM) [Burges, 1998; Cristianini & Shawe-Taylor, 2000], to assist in the diagnosis of neurological and psychiatric pathologies [Fan et al., 2007, 2008a; Kloppel et al., 2008; Lao et al., 2004; Vemuri et al., 2008]. In particular, several methods have been successfully applied to the classification of patients with AD or MCI. These approaches were based on the classification of anatomical features extracted from a set of regions distributed across the whole brain. However, these methods did not include a detailed morphological analysis of the hippocampus, which is affected at the earliest stages of the pathological process and may thus also provide relevant information for the classification of patients. In this paper, we introduce a method to automatically discriminate AD and MCI patients from healthy controls, based on hippocampal shape features. Shape features are extracted using spherical harmonics, a parametric boundary description approach which can be seen as a 3D analog of Fourier series [Gerig et al., 2001a; Kelemen et al., 1999; Styner et al., 2004]. Spherical harmonics coefficients are used as features in a multidimensional classification procedure based on support vector machines.

4.3 Material and methods

4.3.1 Participants

The regional ethics committee approved the study and written informed consent, given by the patients themselves, was obtained from all participants. We studied 23 patients with AD (10 males, 13females, age±standard-deviation (SD)=73±6 years, range=62-81 years, mini-mental score (MMS)=24.4±2.8, range=19-29) and 23 patients with amnestic MCI (10 males, 13 females, age±SD=74±8 years, range=55-87 years, MMS=27.3±1.4, range=24-29) recruited at the Centre Hospitalo-Universitaire (CHU) of Caen. The diagnosis for probable AD was made according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association) criteria [McKhann et al., 1984]. The diagnosis of MCI was based on Petersen et al.'s criteria

4. AUTOMATIC CLASSIFICATION OF PATIENTS WITH ALZHEIMER'S DISEASE BASED ON HIPPOCAMPAL SHAPE FEATURES

[Petersen et al., 2001]. All MCI patients were evaluated every 6 months over an 18-month period to assess conversion, i.e., whether they met NINCDS-ADRDA criteria of probable AD or not. Patients were declared as converters if they had impaired performances (more than 1.5 SD below the normal mean according to age and education when available) in at least one of general intellectual function scales as well as in at least two areas of cognition including memory, leading to impaired daily activities as judged by the clinicians from the consultation interviews. Post hoc exclusion criteria included presence of substantial neurological, psychiatric or any other medical disease that could affect brain functioning or structure, and normal episodic memory performances at follow-up. At completion of the 18-month follow-up period, seven MCI (7/22=32%) patients were declared as converters, 15 patients still had isolated memory deficits (non-converters) and one MCI patient refused follow-up. The annual conversion rate was thus 21%. AD and MCI patients were compared to 25 elderly healthy controls (13 males, 12 females, $age\pm SD=64\pm 8$ years, range=51-84 years) with normal memory performance, as assessed using tests of episodic, semantic and working memory, and without vascular lesions on MRI. To exclude vascular lesions, all controls were checked to have normal signal intensity on T1-, T2- and/or FLAIR-weighted MRI, and notably no substantial white matter T2-FLAIR-weighted hyperintensities (less than 5 pinpoint hyperintensities, size < 4 mm [Meguro et al., 2000]. The controls were screened for the absence of cerebrovascular risk factors, mental disorder, substance abuse, head trauma, substantial MRI or biological abnormality, and incipient dementia using a memory test battery. Control participants were recruited through advertisement in local newspapers. Control participants were required to be over 50 years old. There was no specific sex criterion.

4.3.2 MRI acquisition

Within an interval of two months at most from inclusion for the controls and a few days for MCI and AD patients, each participant underwent a T1-weighted volume MRI scan, which consisted of a set of 128 adjacent axial slices parallel to the anterior commissure-posterior commissure (AC-PC) line and with slice thickness 1.5 mm and pixel size 0.9375×0.9375 mm2 using the spoiled gradient echo sequence (SPGR) (repetition time (TR)=10.3 ms; echo time (TE)= 2.1 ms; field of view (FOV)=24.18 cm2; matrix=256 \times 192). All the MRI data sets were acquired on the same scanner (1.5 T Signa Advantage echospeed; General Electric, Milwaukee, WI).

4.3.3 Automatic hippocampal segmentation

The segmentation of the hippocampus was performed using a fully automatic method we previously developed [Chupin et al., 2008, 2009b; Colliot et al., 2008]. This approach segments both the hippocampus and the amygdala simultaneously based on competitive regiongrowing between these two structures. It includes prior knowledge on the location of the hippocampus and the amygdala derived from a probabilistic atlas and on the relative positions of these structures with respect to anatomical landmarks which are automatically identified.

4.3.4 SPHARM decomposition

Each hippocampus was then described by a series of spherical harmonics, using the SPHARM-PDM (Spherical Harmonics-Point Distribution Model) software developed by the University of North Carolina and the National Alliance for Medical Imaging Computing (http://www.namic.org/Wiki/index.php/Algorithm:UNC:Shape_Analysis). SPHARM are a mathematical approach to represent surfaces with spherical topology, which can be seen as a 3D analog of Fourier series expansion. In brief, the SPHARM approach relied on the following steps. Since the automatic segmentation is based on homotopic deformations, no topological correction was necessary. Hippocampal segmentations were then converted to surface meshes, and a spherical parameterization was then computed using the approach proposed in [Brechbuhler et al., 1995], creating a one-to-one mapping between each point on the surface and each point on a sphere. The surface $v(\theta, \phi) = (x(\theta, \phi), y(\theta, \phi), z(\theta, \phi))$ was decomposed as:

$$\nu(\theta,\phi) = \sum_{l=0}^{\infty} \sum_{m=-l}^{l} c_l^m Y_l^m(\theta,\phi)$$
(4.1)

where the coefficients c_l^m are three-dimensional vectors due to the three coordinate functions, and $Y_l^m(\theta, \phi)$ are spherical harmonics basis functions of degree *l* and order *m*, with $\theta \in [0, \pi]$, $\phi \in [0, 2\pi]$.

They are defined as $Y_l^m(\theta, \phi) = \sqrt{\frac{(2l+1)(l-m)!}{4\pi(l+m)!}} p_l^m(\cos\theta) e^{im\phi}$, where P_l^m are the associated Legendre polynomials. This function family is orthonormal over both l and m:

$$\frac{1}{4\pi} \int_{\theta=0}^{\pi} \int_{\phi=0}^{2\pi} Y_l^m \bar{Y}_{l'}^{m'} \partial\theta \partial\phi = \delta_{ll'} \delta_{mm'}$$

with $\delta_{ij} = 0$ if $i \neq j$, and $\delta_{ii} = 1$ (Kronecker delta).

The series was then truncated at a given degree (here we empirically chose a degree of L = 20 which results in an acceptable degree of smoothing). The coefficients of the series expansion were normalized in order to eliminate effects of rotation and translation: the parameterization was rotated such that the poles of the sphere match with those of the first order ellipsoid (computed from the first three SPHARM coefficients). The SPHARM representation was transformed into a triangulated surface (called the SPHARM-PDM), based on a uniform subdivision of the spherical parameterization.

Each hippocampus was described by a set of 4002 landmarks. The SPHARM-PDM were finally spatially aligned using rigid Procustes alignment. To that purpose, we created a template by averaging all hippocampal surfaces. Specifically, for each of the 4002 landmarks, we computed the arithmetical mean over the whole population. This resulted in an average hippocampal surface formed by the 4002 mean landmarks. Each individual hippocampus was then aligned with respect to that average template. A new template was then formed by averaging the aligned surfaces using the procedure described above. This process was iterated until convergence of the template (i.e. when the template was no longer modified). This alignment resulted in a one-to-one mapping between points of each hippocampus. The corresponding rigid-body transform was then applied to the SPHARM decomposition, resulting in a new set of SPHARM coefficients.

We obtained two types of correspondences between objects:

- SPHARM coefficients, which were entered as features in the SVM classification;
- SPHARM-PDM landmarks, which were used to visualize the localization of shape differences between groups [Styner et al., 2004].

4.3.5 Feature extraction and selection

The classification features were based on the SPHARM coefficients. Specifically, each subject was represented by two sets (one for each hippocampus) of three-dimensional SPHARM coefficients c_l^m . When considering a SPHARM decomposition up to degree 20, each subject can thus be represented by a feature vector of size 2646 which is obtained by concatenating the three coordinates of all coefficients for both sides. Indeed, decomposition up to degree 20 results in $(20 + 1)^2$ vector coefficients. Moreover, there are 2 hippocampi and 3 spatial coordinates. There are thus $2 * 3 * (20 + 1)^2 = 2646$ features. In the following, the vector corresponding to the *k*-th subject is denoted as:

$$x^k = (x_1^k, ..., x_n^k) \in \mathbb{R}^n$$

where n = 2646 is the number of features. Among these features, only some of them convey relevant information for the classification of patients. To identify the most discriminative features for the SVMclassification, we used a univariate feature selection combined with a bagging strategy.We used Student's t-tests in order to determine which features best separate the different populations. In order to obtain a robust selection, the *T* statistics were computed using a bagging approach [Breiman, 1996; Fan et al., 2007]. This approach proceeds as follows: For the i-th feature, we computed the T_i statistics as follows:

- For the *k*-th subject, we computed the $T_i^{(k)}$ statistics from the set $X^{(k)} = X x_k$.
- In order to keep only those features which are always significantly different, we computed $T_i = \min_k T_i^{(k)}$

We repeated this procedure for each of the initial features, and sorted them by increasing T_i . The *p* features which result in the highest T_i values were kept as features in the SVM. The selected features were then centered and normalized using a z-score. In the following, in order to simplify notations, we denote the vector of selected, normalized, sorted, and centered features as $x_k = (x_1^k, ..., x_p^k) \in \mathbb{R}^p$.

4.3.6 Classification using SVM

A support vector machine is a supervised learning method. In brief: given a training set $\{x_k, y_k\}_k = 1, ..., K$, where $x_k \in \mathbb{R}^p$ are observations, and $y_k \in \{-1, 1\}$ are corresponding labels (-1 for controls, 1 for patients for example), linear SVMs search for the optimal hyperplane separating groups, i.e. the hyperplane for which the margin between groups is maximal. To that purpose, the following constrained optimization problem is solved:

subject to
$$\begin{aligned} \min_{w,b,\xi} \frac{1}{2} w^T \cdot w + \sum_{k=1}^{K} \xi^k \\ y^k (w^t \cdot x_k + b) \geq 1 - \xi^k \\ \xi_k \geq 0 \end{aligned}$$

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where *C* is a cost parameter and the ξ_k are positive slack variables allowing some examples to lie on the wrong side of the soft margin. Let the classification function be: f(x) = sign(x.w + b) where *w* determines the orientation of the hyperplane, and *b* the offset from the origin. The vector *w* maximizing the margin can be written as a linear combination of some training examples, called support vectors. The classification function depends only on dot products of the data. SVM can be used to construct nonlinear separations by replacing the dot product with a kernel evaluation into the original problem. Here, we chose to use Radial Basis Functions kernels (RBF):

$$K_{\gamma}(u,v) = e^{-\gamma ||u-v||^2},$$
(4.2)

where the parameter γ controls the width of the kernel. We also compared the performance of the RBF kernel with that of a linear kernel. The SVM implementation relied on the LIBSVM Library (http://www.csie.ntu.edu.tw/~cijlin/libsvm). More details on SVM can be found in [Cristianini & Shawe-Taylor, 2000].

4.3.7 Validation

Classification accuracy (proportion of subjects correctly classified among the whole population), error (proportion of subjects wrongly classified), sensitivity (proportion of AD or MCI patients correctly classified) and specificity (proportion of healthy controls correctly classified) were computed using leave-one-out cross-validation. To avoid introducing bias in the feature selection, the feature selection step detailed above was integrated in the leave-one-out procedure. In this procedure, each subject was successively selected as the test subject and all remaining subjects were used for the feature selection and classifier training. To estimate the optimal parameters *C* and γ of the SVM, we used a grid-search with values ranging from $C = 2^0, ..., 2^20$ and $\gamma = 2^-15, ..., 2^0$. We computed the classification accuracy for different number of selected features (corresponding to different thresholds on the p-value of the *T* statistic).

4.3.8 Comparison with a voxel-based SVM approach

We compared our approach to that proposed by [Kloppel et al., 2008] in the same context of automatic classification of patients with AD. Kloppel et al. [2008] propose two different versions of their approach: one is based on whole-brain data and the other includes only data from a region of interest (ROI) located in the anterior medial temporal lobe, including part of the hippocampus. This allows comparing the accuracy of our approach to both a whole-brain approach and an approach restricted to the hippocampal region. In brief, the approach of [Kloppel et al., 2008] relied on the following steps. Images were first segmented into gray matter (GM), white matter and cerebrospinal fluid using SPM5 (Statistical Parametric Mapping, Institute of Neurology, University College London, London, UK). Then, GM segmentations were further normalized to the population templates generated from all the images involved in each classification experiment (i.e. all AD and control subjects for the AD vs controls classification experiment, all MCI and controls for MCI vs controls classification), using the DARTEL diffeomorphic registration algorithm [Ashburner et al., 2007]. Tissue classes were then modulated to ensure that the overall amount remained
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constant. No spatial smoothing was performed. Kernel matrices were then created from normalized GM segmented images and used to classify patients using linear and RBF SVM. The classification was then performed using the two different types of analysis: the first one using whole-brain data and the second one using data from a hippocampus-centered ROI. Leave-one-out accuracies were optimized with respect to C and γ with the same range of parameters as in our method. In our method, we selected the optimal number of features based on multiple leave-one-out experiments. This can introduce a bias in the evaluation. No such bias is present in Kloppel et al's method. In order to fairly compare these two approaches, we need to evaluate our method without the bias concerning the number of selected features. We therefore tested both approaches on a completely separate group, while computing the threshold on the p-value for feature selection on the original group. To that purpose, we randomly selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI) 25 AD patients (age: $75\pm$ 6 years, MMS=23.3±2), 25 patients with amnestic MCI (age:75±5 years, MMS=26.6±1.8), and 26 elderly cognitively normal individuals (age: 75±4 years, MMS=28.9±1.3). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, M.D., VA Medical Center and University of California - San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research - approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For up-to-date information see www.adni-info.org.

The complete classification procedure was the same as before, apart from feature selection. For feature selection, instead of optimizing the number of features, we used the optimal p-value computed for the original group (p = 0.002) and applied it directly to the ADNI group. There is no bias in this selection since no data from the ADNI group was used to compute the p-value threshold. We also tested the performance obtained on the original group when the optimal p-value is computed on the ADNI group.

4.3.9 Comparison with classification approaches based on SPHARM-PDM

We compared the accuracy of classification based on SPHARM to that of classification based on the SPHARM-PDM. To that purpose, we performed two experiments. In the first experiment, we applied to the SPHARM-PDM the same univariate feature selection strategy that we used in our method for the SPHARM coefficients. We computed the classification accuracies obtained with a SVM, for varying numbers of features. In the second experiment, the dimensionality of the SPHARM-PDM was reduced using principal component analysis (PCA). The resulting eigenvectors were ranked by decreasing order according to their corresponding eigenvalues. We computed the classification accuracies obtained with a SVM, for varying numbers of eigenvectors. We also compared our approach to that proposed by [Shen et al., 2003a]. This approach relied on the following steps: each hippocampus was described by a set of SPHARM-PDM landmarks (the number of landmarks was 642 as described in [Shen et al., 2003a]. The dimensionality of the SPHARM-PDM was reduced using PCA. The eigenvectors were ranked in decreasing order. Fisher's Linear Discriminant (FLD) was used as a classifier. This is quite similar to the experiment performed above except that it relies on FLD instead of SVM. As indicated in [Shen et al., 2003a], two experiments (one for the left hippocampi, the other for the right) were performed, and classification was computed while letting the number of principal components (PC) vary.

4.3.10 Statistical group analysis using SPHARM-PDM

In order to illustrate the behaviour of the SPHARM approach for the detection of local hippocampal abnormalities, we used the SPHARM-PDM to perform a statistical group analysis investigating the differences between AD/MCI patients and healthy controls. It should be noted that this analysis is presented here only for illustrative purposes, in order to compare the behaviour of SPHARM with other hippocampal morphometric studies in AD, and that the SPHARM-PDM were not used for the classification of subjects. To test for group differences in the spatial location (*x*, *y*, *z*) at each vertex of the hippocampal surface, we used the multivariate Hotelling T^2 metric [Styner et al., 2006]. For each group, the mean μ_i and the covariance matrix Σ_i of the spatial location were computed. Then the modified T^2 metric at each vertex was given by:

$$T^{2}(\mu_{1}-\mu_{2})^{T}\left(\frac{1}{K_{1}}\Sigma_{1}+\frac{1}{K_{2}}\Sigma_{2}\right)^{-1}(\mu_{1}-\mu_{2})$$
(4.3)

where K_i is the number of subjects of the *i*-th group. p-values were obtained via permutation tests. This analysis was repeated at each vertex, resulting in a significance map, which shows local group differences. The p-values were corrected for multiple comparisons using a permutation-based approach [Styner et al., 2006].

4.4 Results

4.4.1 Classification results

The classification accuracy for a varying number of features is shown on Figures 4.1 and 4.2. For AD vs controls classification, the best classification was obtained for a number of features between 16 and 22 (which corresponds to a p-value of 0.002), giving a correct classification



Figure 4.1: AD vs controls classification. The classification accuracy is shown as a function of the number of selected features. Using a SVM with a RBF kernel gives the highest accuracy (94%), for a number of features between 16 and 22.



Figure 4.2: MCI vs controls classification. The classification accuracy is shown as a function of the number of features. Using a SVM with a RBF kernel gives the highest accuracy (83%), with a number of features between 2 and 3



Figure 4.3: Classification rates for AD vs controls, as a function of the parameters C and γ . The following results are shown: accuracy, error, sensitivity and specificity. A "grid-search" approach was conducted in order to select the best parameters. The cost parameter C ranges from 2⁰ to 2²⁰. The parameter γ , corresponding to the width of the RBF kernel, ranges from 2⁻¹⁵ to 2⁰. Results are displayed for the classifier with 19 features, for which the best performance is obtained.

rate of 94%, a sensitivity of 96%, and a specificity of 92%. For MCI vs controls, the best classification was obtained for a number of features between 2 and 3 (which also corresponds to a p-value of 0.002), giving a correct classification rate of 83%, a sensitivity of 83%, and a specificity of 84%. The accuracy of the RBF classifier was always superior (or equal) to that of the linear classifier. Figures 4.3 and 4.4 show the classification accuracy for different values of the parameters C and γ , for an optimal number of features (i.e. 19 for AD, 3 for MCI). There is a substantially large set of values which lead to optimal accuracy.

To assess the influence of the degree of decomposition on the classification performance, we repeated the selection and classification procedure with different values of maximal degree L (L=5, L=10, L=15, L=20). For AD vs controls classification, the accuracy was 92% for L=5 and L=10, and 94% for L=15 and L=20. For MCI vs controls classification, the accuracy was 83% for L=5, 10, 15 and 20.

SPHARM coefficients cannot be used directly to visualize the localization of shape changes because SPHARM basis functions have a global support across the sphere. Thus, coefficients are not associated to a localized area, but rather to a mode of deformation. To illustrate the influence of discriminative coefficients on hippocampal shape, we created a

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Figure 4.4: Classification rates for MCI vs controls, as a function of the parameters C and γ . The following results are shown: accuracy, error, sensitivity and specificity. A "grid-search" was conducted in order to select the best parameters. Results are displayed for a classifier with 3 features, for which the best performance is obtained.

mean shape by averaging all coefficients across the AD and controls group. We chose the two most discriminative coefficients for the AD vs controls separation. We then illustrated the modes of variation by adding or subtracting 2 SD of these two most discriminative coefficients (Figure 4.5).

4.4.2 Comparison with a voxel-based SVM approach

The comparison between our approach and the one proposed by Kloppel et al. [2008] is presented in Table 4.1. On the ADNI group, our method reached 88% accuracy, 84% sensitivity and 92% specificity for AD vs controls and 80% accuracy, 80% sensitivity and 80% specificity for MCI vs controls. For AD vs controls classification, the accuracy reached by Kloppel's method (90%) was similar to that of our approach. For MCI vs controls, the accuracy was 71% which is substantially lower than our results. When the optimal p-value was computed on the ADNI group and applied to the original group, our method reached 88% accuracy, 91% sensitivity and 84% specificity for AD vs controls and 79% accuracy, 78% sensitivity and 80% specificity for MCI vs controls. Thus, the results obtained when selecting the p-value on the ADNI group or on the original group are very similar.



Figure 4.5: Illustration of the influence of the two most discriminative SPHARM coefficients on hippocampal shape for AD vs controls classification. A mean shape was created by averaging all coefficients across the AD and controls group. To illustrate the modes of variation, we added or substracted to the shape 1 SD or 2 SD of the two discriminative coefficients.

	Our me	ethod	Kloppel's	whole brain	Kloppe	's ROI
Type of kernel	Linear	RBF	Linear	RBF	Linear	RBF
AD vs controls	86%	88%	90%	90%	84%	86%
MCI vs controls	78%	80%	63%	63%	71%	71~%

Table 4.1: Comparison between our approach and the method proposed in [Kloppel et al.,2008] on the ADNI group.

4.4.3 Comparison with classification approaches based on SPHARM-PDM

Using the SPHARM-PDM, univariate feature selection and SVM classification, we obtained the following results. AD vs controls classification reached 92% which is similar to our approach. For MCI vs controls, the accuracy reached 75% which is substantially lower than that obtained with our approach based on SPHARM coefficients (83%). Using the SPHARM-PDM, PCA and SVM classification, we obtained the following results. For AD vs controls, the best result was obtained for 15 eigenvectors, giving a correct classification rate of 94% which is the same as for the SPHARM coefficients. For MCI vs controls, the best result was obtained for five features, giving a correct classification rate of 69% which is substantially lower than with our approach.

For AD vs controls, the method proposed by [Shen et al., 2003a] achieved 92% accuracy for the left hippocampi (using between 9 and 11 PC) and 96% for the right hippocampi (using 24 PC). For MCI vs controls, accuracy was 67% for the left hippocampi (with 11 PC) and 73% for the right hippocampi (8 PC), which is lower than with our approach. Therefore, using SPHARM coefficients seems more efficient than using the PDM to discriminate between MCI patients and controls.

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Figure 4.6: Group differences between AD and controls. Regions with statistically significant atrophy (p < 0.05) are displayed in colors ranging from yellow to red, blue areas correspond to regions with no significant differences. p-values are corrected for multiple comparisons. The medial aspect of the head and the lateral aspect of the body, approximately corresponding to the CA1 subfield, are affected by deformations in AD patients.



Figure 4.7: Group differences between MCI and controls. Regions with statistically significant atrophy (p < 0.05) are displayed in colors ranging from yellow to red, blue areas correspond to regions with no significant differences. p-values are corrected for multiple comparisons. The patterns of atrophy are similar to those of the AD vs controls comparison but with a smaller spatial extent.

4.4.4 Statistical group analysis using SPHARM-PDM

The maps of group differences between AD/MCI patients and controls are shown in Figure 4.6 and 4.7. For the AD vs controls comparison, the most significant deformations are shown in the medial part of the head of the hippocampus, and in a region approximately corresponding to CA1 subfield. CA2 and CA3 regions are relatively spared. Similar but less extended patterns

are found for the MCI vs controls comparison.

4.5 Discussion

In this paper, we proposed a new approach to automatically discriminate patients with Alzheimer's disease and MCI from normal aging, based on multidimensional classification of hippocampal shape features. The SVM-based classification resulted in a high degree of accuracy.

Hippocampal shape features were extracted by expanding hippocampal surfaces into series of spherical harmonics (SPHARM). SPHARM have been applied to study morphological abnormalities of brain structures in several pathologies. However, it has been mainly used to assess group differences [Gerig et al., 2001a; Shi et al., 2007; Styner et al., 2004] rather than to assist individual diagnosis. Gerig et al. [2001b] individually classified patients with schizophrenia using the mean square distance (MSD) derived from SPHARM. However, using the MSD leads to a univariate classification in which the relationships between coefficients are not taken into account. Shen et al. [2003b] used the SPHARM-PDM landmarks as features to classify patients with schizophrenia. Here, we relied on SPHARM coefficients (and not on the SPHARM-PDM) to extract features which were used in a multidimensional SVMbased classification method. These coefficients are well suited to building classification features because they provide a multi-scale representation and thus the different features correspond to different levels of detail. In particular, the first features concentrate a lot of geometrical information. This property may be related to the fact that a relatively small number of features was sufficient to discriminate between subjects. On the other hand, it is likely that each isolated SPHARM-PDM landmark does not convey a lot of information and that a larger number of features would be necessary for the discrimination. To robustly select relevant features among the whole set of coefficients, we used a bagging strategy and leave-one-out cross-validation was performed to evaluate accuracy. Our approach achieved classification accuracies of 94% for AD vs controls, 83% for MCI vs controls. These rates are higher to that reported for manual hippocampal volumetry in various studies, in particular for the MCI patients. Indeed, while manual hippocampal volumetry can discriminate AD patients from controls with a high degree of accuracy, ranging from 82% to 90% [Frisoni et al., 1999; Jack et al., 1992; Laakso et al., 1998; Lehericy et al., 1994; Xu et al., 2000], the accuracy obtained for MCI patients is usually much lower, ranging from 60% to 74% [Convit et al., 1997; De Santi et al., 2001; Du et al., 2001; Pennanen et al., 2004; Xu et al., 2000]. Thus, taking into account shape deformations seems to result in a higher discriminative power than considering only volume, which is a global marker of atrophy. Moreover, most volumetric studies previously relied on manual segmentation, which is time-consuming and requires specific training and is thus not suitable to clinical practice. To overcome this difficulty, we segmented the hippocampi with recently developed fully automatic software. Thus, the procedure presented in this paper, from hippocampal segmentation to classification, is fully automatic and does not require user intervention. The optimal classification was obtained for a number of features comprised between 16 and 22 for AD patients and between 2 and 3 for MCI patients. Interestingly, these numbers of features correspond to approximately the same statistical threshold (p=0.002). This implies that, at a given statistical threshold, there

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are more discriminative features for AD patients than for MCI patients, which reflects the fact that atrophy is greater in AD than MCI. Thus, there are more useful features for the SVM in the case of AD patients than for MCI. When irrelevant features are added, the performance of the classifier drops. Besides, the accuracy of the RBF classifier was always superior (or equal) to that of the linear SVM. This suggests that the best separation of our data is nonlinear. Moreover, the fact that the RBF was always at least as good as the linear SVM may be related to the asymptotic behaviour of RBF. Indeed, as shown by [Keerthi & Lin, 2003], when γ is close to zero and $C = \frac{\hat{C}}{2\gamma}$ where \hat{C} is fixed, then the RBF classifier converges to a linear SVM with penalty parameter \hat{C} . As a result, when a complete search for parameters γ and C has been performed (which was the case in our study), the RBF classifier is at least as accurate as the linear SVM [Keerthi & Lin, 2003].

Furthermore, there is a substantially large range of optimal values for parameters C and γ of the SVM. This suggests that the approach is relatively robust to the choice of these parameters. However, leave-one-out cross-validation accuracies can be optimistic, since the search for optimal parameters, as well as the selection of the number of features, occurred outside of the leave-one-out loop. As a consequence, the information about each left-out subject could help in the selection of optimal parameters C and γ , and the number of features. To be fully representative of the generalization performance, the accuracy should be computed using a three-way split. However, the relatively small sample size in our study forbids us from conducting a three-way split procedure. This is also the case in [Fan et al., 2007] which reports leave-one-out accuracies. On the contrary, in [Vemuri et al., 2008], the test data was completely isolated from the data that was used for parameter selection. The accuracy was not heavily influenced by the degree of the SPHARM decomposition. For AD vs controls, the results were identical for degrees 15 and 20 and very similar for degrees 5 and 10. For MCI vs controls, the results were the same for degrees 5, 10, 15 and 20. Indeed, the selected coefficients had a degree inferior or equal to 4. Nevertheless, even if for MCI lower degrees led to a good accuracy, it still seems preferable to use a decomposition of a relatively high degree (probably around 15) in order to ensure an accurate registration of shapes.

Although lesions start in the medial temporal lobe, atrophy is also present in a distributed pattern of brain regions, including the temporal neocortex, the cingulate gyrus, the precuneus, the temporo-parietal association and the perisylvian association [Baron et al., 2001; Chetelat et al., 2002, 2005; Karas et al., 2003; Lerch et al., 2005]. Several authors have thus recently proposed to classify patients based on whole-brain data and not only from a single structure [Fan et al., 2008a; Kloppel et al., 2008; Vemuri et al., 2008]. In these approaches, the SVM uses structural features which are extracted from a set of anatomical regions distributed across the brain. The reported classification accuracies range from 89% to 96% [Fan et al., 2008a; Kloppel et al., 2008; Vemuri et al., 2008] for AD vs controls discrimination, and from 82% to 90% for MCI vs controls [Davatzikos et al., 2008a; Fan et al., 2008a]. Using a different strategy in which SVM features are formed from the hippocampus only, we achieved similar classification rates (94% for AD patients, 83% for MCI patients). Our approach, based on a detailed shape analysis but restricted to a single structure, and these whole-brain methods, which use extensive but less detailed information, seem complementary. Ultimately, it seems interesting to combine these approaches in an integrated classification method. The AD cases included in our study were less severely affected (mean MMS=24) than those studied in [Kloppel et al., 2008] (mean MMS=17) and in [Vemuri et al., 2008] (median MMS=20). It should be noted that the patients studied by [Kloppel et al., 2008] were pathologically confirmed. The disease severity of our AD and MCI patients was similar to those included in [Fan et al., 2008a] (mean MMS=23 for AD and 27 for MCI) and in [Davatzikos et al., 2008a] (mean MMS=26 for MCI). We compared our approach to that proposed by [Kloppel et al., 2008]. Kloppel et al. [2008] propose two different versions of their approach: one is based on whole-brain data and the other includes only data from a region of interest (ROI) located in the anterior medial temporal lobe, including part of the hippocampus. In order to perform a fair comparison between our approach and theirs, we determined the optimal threshold for feature selection on the original group of subjects and used a completely separated group for the evaluation. For MCI vs controls classification, the accuracies obtained with their method were lower than with our approach (63% for whole-brain, 71% for hippocampal ROI, compared to 80% for our method). For AD vs controls, the accuracy of their wholebrain method increased to 90%, which is slightly superior to our results (88%). This comparison experiment should be confirmed in larger groups of patients. However, these results indicate that a specific analysis of hippocampal shape may be more sensitive than an approach using a ROI, defined at the group level, to discriminate MCI patients from controls. Indeed, using a specific segmentation method dedicated to the hippocampus allows precisely defining the boundaries of this structure in each individual subject. On the contrary, [Kloppel et al., 2008] use a region of interest defined at the group level which also encompasses other structures. Nevertheless, whole-brain methods, such as the one proposed by [Kloppel et al., 2008], are likely to be more efficient to discriminate between different types of dementia. In particular, [Kloppel et al., 2008] and [Davatzikos et al., 2008b] successfully applied whole-brain approaches to the differentiation of patients with AD and FTLD (fronto-temporal lobar degeneration). We also compared our approach based on SPHARM coefficients to classifications based on SPHARM-PDM. First, we compared our approach to a classification based on SVM and SPHARM-PDM. Second, we performed a comparison with the approach of [Shen et al., 2003a] which uses a FLD classifier. In both cases, our approach reached a higher accuracy for MCI vs controls classification. This suggests that using the coefficients is more efficient than using the PDM to discriminate between MCI patients and controls.

Although ADNI MCI patients are slightly more impaired than ours (mean MMSE=26.6 vs 27.3, respectively), this difference was not statistically significant (p=0.13), and the classification results obtained on our data were very close to those obtained on ADNI data. Most studies of hippocampal shape in AD were restricted to group analysis and not to the discrimination of individual patients [Apostolova et al., 2006a,b; Chételat et al., 2008; Csernansky et al., 2000; Frisoni et al., 2006; Shen et al., 2005; Wang et al., 2006] with the exception of [Csernansky et al., 2000] in which the high-dimensional brain mapping (HDBM) approach was used to obtain hippocampal volumes and hippocampal shape differences between patients with very mild AD and controls. Using a classification based on both volume and shape features, they achieved a sensitivity of 83% and a specificity of 78%, which is lower than those obtained in our study. Moreover, they did not investigate the discrimination of MCI patients from controls. Another exception is [Li et al., 2007] who proposed a method for shape analysis of the hippocampus based on SVM. An important difference between their approach and ours is that their features represent the average deformation of a surface patch from a mean surface. For AD vs controls classification, their reported accuracies are similar to ours (between 84% and 94%). However, it should be noted that the AD patients

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included in their study are at a more severe stage than ours (MMS=19 vs 24). Moreover, they did not investigate the classification of MCI patients. Using SPHARM-PDM, we studied the localization of hippocampal shape changes between AD or MCI patients and controls. We found that AD patients exhibit a spatial pattern of deformations that approximately corresponds to the CA1 subfield of the hippocampus. CA2 and CA3 are relatively spared. In MCI patients, a similar but less extended spatial pattern was found. Although our method cannot provide a direct mapping of hippocampal subfields since these are below the resolution of conventional MRI, this is in concordance with histopathological studies which demonstrated that neurofibrillary tangles and neuronal loss predominate in the CA1 subfield [Hyman et al., 1984; Van Hoesen & B.T., 1990]. Previous hippocampal morphometric studies in AD have relied on different types of methodologies: the high-dimensional brain mapping (HDBM) approach [Csernansky et al., 2000; Wang et al., 2006], radial mapping [Apostolova et al., 2006b; Frisoni et al., 2006] and a voxel-based method [Chételat et al., 2008]. Their main finding is that atrophy is predominant in the CA1 region. The results of our study require confirmation in larger groups of participants. However, the use of a bagging strategy brings robustness to the feature selection. Nevertheless, the relatively small size of the samples may explain why the classification accuracy diminishes when less relevant features are added, in particular for MCI patients. In order to keep the control group as large as possible, we decided not to exclude control participants based on age. As a consequence, the mean age of the controlswas significantly lower (p < 0.001) than those of the AD and MCI patients. However, it should be noted that misclassified controls were not always among the oldest. The misclassified controls were respectively 53 and 84 years old for AD vs controls classification, and 59, 67, 70 and 84 years for MCI vs controls classification. Nevertheless, further studies on larger age-matched groups of participants are required to confirm our results. Moreover, we could not investigate the classification of converters vs non-converters, due to the small number of converters. Indeed, MCI is a heterogeneous population and not all MCI patients have prodromal AD. Further studies on larger groups of longitudinally followed MCI patients are needed to assess whether our method can identify patients with incipient AD in an MCI population. Using multidimensional classification of hippocampal shape features, we were able to individually classify Alzheimer's disease, MCI and control participants with a high degree of accuracy. This method may become a useful tool to assist in the diagnosis of Alzheimer's disease.

4.6 Acknowledgments

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CHAPTER

EVALUATION ON A LARGE DATABASE

In this chapter, we present an evaluation of the method proposed in the previous chapter to a larger population of 509 subjects from the ADNI database. We evaluated the sensitivity and specificity of the approach for three classification experiments. The first one is the classification between patients with Alzheimer's disease (AD) and cognitively normal subjects (CN). The second experiment is the classification between patients with mild cognitive impairment (MCI) who converted to AD (within a 18 months period) and CN. This corresponds to the detection of patients with prodromal AD [Dubois & Albert, 2004]. The third experiment is the classification between MCI patients who converted to AD within 18 months and MCI patients who did not convert within the same period. This evaluation of our method was performed as part of a more comprehensive study, in collaboration with Rémi Cuingnet, which compared 10 methods for the classification of patients with AD and MCI. Within this study, three main categories of methods were evaluated: methods based on voxel-based measures, methods based on cortical thickness, methods based on the hippocampus. My contribution to this work was on the experiments that concerned the hippocampus (application of the methods to this dataset, statistical analysis) and discussion of the results.

This work was published in the following paper: R. Cuingnet, **E. Gerardin**, J. Tessieras, G. Auzias, S. Lehéricy, M.-O. Habert, M. Chupin, H. Benali, O. Colliot, The ADNI, Automatic classification of patients with Alzheimer's disease from structural MRI: a comparison of ten methods using the ADNI database. *NeuroImage*, 15;56(2):766-81, 2011.

Instead of reproducing the entire paper here, we prefered to focus on the experiments that concerned the hippocampus, along with some elements of comparison with the other methods. The full text of the original article can be found in the appendix.

5.1 Material

5.1.1 The ADNI database

Data used in the preparation of this chapter were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). The ADNI is a 5-year public-private partnership launched in 2003. The primary goal of this multicentric study has been to test whether markers from multiple sources (markers from MRI or PET, biological markers from blood or CSF, clinical and neuropsychological data) can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

About 800 participants are recruited for the study. Among these subjects, we can count about 200 cognitively normal elderly controls (CN), 400 subjects with mild cognitive impairment (MCI), and 200 subjects with LAzheimer's disease (AD). The criteria used for the inclusion of participants were those defined in the ADNI protocol (described in details at http://www.adni-info.org/Scientists/AboutADNI.aspx).

5.1.2 Participants

We selected all the subjects for whom preprocessed images were available at the beginning of this work. As a result, 509 subjects were selected: 162 cognitively normal elderly controls (CN), 137 patients with AD, 76 patients with MCI who had converted to AD within 18 months (MCIc) and 134 patients with MCI who had not converted to AD within 18 months. We did not consider MCI patients who had been followed less than 18 months and had not converted within this time frame. The 509 images came from 41 different centers. Clinical and demographic characteristics of the studied population are given in Table 5.1.

To assess differences in demographic and clinical characteristics between groups, we used Student's t-test for age and Pearson's chi-square test for gender. Significance level was set at 0.05. No significant differences were found.

In order to obtain unbiased estimates of the performances, the set of participants was then randomly split up into two groups of the same size: a training set and a testing set. The algorithms were trained on a training set and the measures of the diagnostic sensitivity and specificity were carried out with an independent test set. The division process preserved the age and sex distribution.

Demographic characteristics of the studied population selected from the ADNI database are presented in Table 5.1.

5.1.3 MRI acquisition

The MR scans are T1-weighted MR images. MRI acquisition had been done according to the ADNI acquisition protocol in [Jack et al., 2008]. For each subject, we used the MRI scan from the baseline visit when available and from the screening visit otherwise. We only used images

Set	Diag.	Nb.	Age	Sex	MMS
Training set	CN	81	$76.1 \pm 5.6 \ [60 - 89]$	38 M / 43 F	29.2 ± 1.0 [25 – 30]
	AD	69	$75.8 \pm 7.5 \ [55 - 89]$	34 M / 35 F	$23.3 \pm 1.9 \; [18 - 26]$
	MCIc	39	74.7 ± 7.8 [55 – 88]	22 M / 17 F	$26.0 \pm 1.8 \ [23 - 30]$
	MCInc	67	$74.3 \pm 7.3 \; [58 - 87]$	42 M / 25 F	$27.1 \pm 1.8 \ [24 - 30]$
Testing set	CN	81	$76.5 \pm 5.2 [63 - 90]$	38 M / 43 F	$29.2\pm 0.9 [26-30]$
	AD	68	$76.2 \pm 7.2 [57 - 91]$	33 M / 35 F	23.2 ± 2.1 [20 – 27]
	MCIc	37	$74.9 \pm 7.0 \; [57 - 87]$	21 M / 16 F	$26.9 \pm 1.8 \; [24 - 30]$
	MCInc	67	$74.7 \pm 7.3 \; [58 - 88]$	42 M / 25 F	$27.3 \pm 1.7 \ [24 - 30]$
Whole set	CN	162	$76.3 \pm 5.4 [60 - 90]$	76 M / 86 F	$29.2 \pm 1.0 \; [25 - 30]$
	AD	137	$76.0 \pm 7.3 \; [55 - 91]$	67 M / 70 F	$23.2\pm2.0[18-27]$
	MCIc	76	74.8 ± 7.4 [55 – 88]	43 M / 33 F	$26.5 \pm 1.9 \; [23 - 30]$
	MCInc	134	$74.5 \pm 7.2 \ [58 - 88]$	84 M / 50 F	$27.2 \pm 1.7 \ [24 - 30]$

Table 5.1: Clinical and demographic characteristics of the population study. Values are given as mean \pm std [min-max].

acquired at 1.5T. To enhance standardization across sites and platforms of images acquired in the ADNI study, pre-processed images that have undergone some post-acquisition correction of certain image artifacts are available [Jack et al., 2008]. We used images with the following pre-processing steps :

- gradwarp correction: image geometry correction for gradient nonlinearity
- B1 non-uniformity correction: correction for intensity non-uniformity due to nonuniform receiver coil sensitivity

These two preprocessing steps can be performed directly on the MRI console and thus seem feasible in clinical routine.

All subjects were scanned twice at each visit. As explained in [Jack et al., 2008], MR scans were graded qualitatively by the ADNI investigators of the ADNI MRI quality control center at the Mayo Clinic for artifacts and general image quality. Each scan was graded on several separate criteria: blurring/ghosting, flow artifact, intensity and homogeneity, signal-to-noise ratio (SNR), susceptibility artifacts, and gray-white/cerebrospinal fluid contrast. For each subject, we used the MRI scan which was considered as the best quality scan by the ADNI investigators. In the description of the ADNI methods (http://www.loni.ucla.edu/ADNI/Data/ADNI_Data.html), the best quality image is the one which was used for the complete pre-processing steps. We thus used the images which had been selected for the complete pre-processing pipeline. No other exclusion criteria based on image quality were applied.

5.2 Methods

5.2.1 Classification experiments

Three classification experiments were performed. The first one is the classification between CN subjects and patients with probable AD and is referred to as *CN vs AD* in the following. The second one is the classification between CN subjects and MCI converters and is referred to as *CN vs MCIc*. It corresponds to the detection of patients with prodromal AD as defined by [Dubois & Albert, 2004]. Indeed, MCI patients who will convert to AD are, at baseline, patients with incipient AD but non-demented, i.e. patients with prodromal AD. The third one is the classification MCInc versus MCIc and is referred to as *MCInc vs MCIc*. It corresponds to the prediction of conversion in MCI patients.

5.2.2 Method based on the hippocampus

We tested three approaches based on hippocampal features: two of them are based on hippocampal volume, the third one being the method based on hippocampal shape presented in the previous chapter.

We first tested the classification accuracy obtained when the only feature is the hippocampal volume. The segmentation of the hippocampus was performed using the fully automatic method SACHA developed by our group [Chupin et al., 2007, 2009b,a], as in the previous chapter. For each subject, we computed the volume of the hippocampi. Volumes were normalized by the total intracranial volume (TIV) computed by summing SPM5 segmentation maps of grey matter, white matter, and cerebrospinal fluid (CSF), inside a bounding box defined in standard space to obtain a systematic inferior limit. For more robustness with respect to segmentation errors, left and right volumes were averaged. This approach is referred to as "Hippo-Volume-S" the following.

We also evaluated this approach with the hippocampal volume obtained with the FreeSurfer image analysis suite and corrected with the total intracranial volume also obtained with obtained with FreeSurfer. This approach will be referred to as "Hippo-Volume-S".

We then tested the method based on hippocampal shape described in the previous chapter. The different steps are the same previously: the segmentation of the hippocampus is performed using SACHA, then its shape is modeled by a series of spherical harmonics coefficients. The only difference is in the feature selection step: in the study described in the previous chapter, we used a feature selection step because the subjects groups were much smaller (less than 30 subjects in each group). When the number of subjects is small, the classifier can be more sensitive to uninformative features. In the present study, the number of subjects is larger and thus a feature selection step is less necessary and increases the risk of overfitting. We thus chose to avoid this selection step. We also tested the procedure with the selection step but it did not lead to further improvement in this study. Moreover, the degree of the SPHARM decomposition was set at four. Four subjects were not successfully processed by the SPHARM pipeline. They could thus not be classified with the SVM and were excluded from the training set. For the testing set, those subjects were considered as 50% misclassified.

5.2.3 Other methods included in the comparison study

Recently, several high dimensional classification methods have been proposed as new tools for the early diagnostic of Alzheimer's disease (AD) or mild cognitive impairment (MCI) based on T1-weighted MRI [Chupin et al., 2009a; Colliot et al., 2008; Davatzikos et al., 2008a; Desikan et al., 2009; Fan et al., 2005, 2007, 2008a,b; Hinrichs et al., 2009; Kloppel et al., 2008; Magnin et al., 2009; Misra et al., 2009; Querbes et al., 2009; Vemuri et al., 2008].

As part of a comparison study [Cuingnet et al., 2011], we compared ten methods on the same population of 509 subjects from the ADNI database. Three of the methods use the hippocampus and have been described above. Here, we describe very briefly the seven others. A more comprehensive description can be found in [Cuingnet et al., 2011].

These seven other methods can be grouped into two categories: voxel-based methods in which the features are tissue probabilities computed at each voxel, and vertex-based methods in which the features are thickness measurements computed at each vertex of the cortical surface.

For voxel-based methods, tissue probabilities maps (GM, CSF, WM) were generated using the SPM5 (Statistical Parametric Mapping, London, UK) unified segmentation routine [Ashburner & Friston, 2005]. Features were defined in stereotaxic space using either direclty the SPM5 unified segmentation result or using the DARTEL diffeomorphic registration algorithm [Ashburner et al., 2007]. Four main voxel-based methods were then tested. The first one considers the voxels of the tissue probability maps directly as features in the classification [Kloppel et al., 2008]. This type of approach is referred to as "Voxel-Direct" in the following. The second method is based on the STAND-score approach proposed in [Vemuri et al., 2008], in which the dimensionality is reduced by a sequence of feature aggregation and selection steps. This approach is referred to as "Voxel-STAND". The third approach consists in grouping the voxels into anatomical regions using a labeled atlas. This type of approach was used [Lao et al., 2004; Magnin et al., 2009]. Such an approach will be referred to as "Voxel-Atlas". The fourth method is the COMPARE approach proposed in [Fan et al., 2007, 2008a,b] and relies on a parcellation that is adapted to the pathology. In the following, we refer to this approach as "Voxel-COMPARE".

For vertex-based methods, the features are the cortical thickness values at each vertex of the cortical surface. Cortical thickness measures were performed with the FreeSurfer image analysis suite (Massachusetts General Hospital, Boston, MA, http://surfer.nmr.mgh.harvard.edu/). Four subjects were not successfully processed by the FreeSurfer pipeline. Those subjects are marked by an asterisk in Tables S2 to S9 (**see appendix**). They could thus not be classified with the SVM and were excluded from the training set. For the testing set, the subjects were considered as 50% misclassified.

Three main vertex-based methods were then tested. The first one considers cortical thickness values at every vertex directly as features in the classification with no other preprocessing step. This approach is referred to as "Thickness-Direct" the following. In the second method, vertices are grouped into anatomical regions using an atlas. This approach is referred to as "Thickness-Atlas" in the following. The third method involves a combination of neocortical and non-neocortical ROIs by wrapping an anatomical atlas. The regions used were that of [Desikan et al., 2009]: the entorhinal cortex thickness, the supramarginal gyrus thickness and the hippocampal volume. This approach is referred to as "Thickness-ROI" in the following. These methods are summarized in Table 5.2.

5.2.4 Classification methods

5.2.4.1 Classifiers

We used a linear C-SVM for all the approaches except COMPARE [Fan et al., 2007] for which a non-linear C-SVM with a Gaussian kernel was used. The SVM implementation relied on the LIBSVM Library [Chang & Lin, 2001]. The dimension of the features of the approach Hippo-Volume is only one. Therefore a much simpler classifier can be used with no hyperparameter: each participant is assigned to the closest group. Specifically, if S1 and S2 are two groups of participants with respective centers of mass defined as m_1 and m_2 , a new individual with hippocampus volume x is assigned to the closest group according to its Euclidean distance to the center of mass. As in [Desikan et al., 2009] a logistic regression is used instead of a SVM, the classification step of Thickness-ROI was also based on a logistic regression.

5.2.4.2 Evaluation

In order to obtain unbiased estimates of the performances, the set of participants was randomly split into two groups of the same size: a training set and a testing set. The training set was used to determine the optimal values of the hyperparameters of each method and to train the classifier. The testing set was then only used to evaluate the classification performances. The training and testing sets were identical for all methods, except for those four cases for which the cortical thickness pipeline failed and those other four for which the SPHARM pipeline failed. For the SPHARM and the cortical thickness methods, the subjects for whom the corresponding pipeline failed could not be classified with the SVM and were therefore excluded from the training set. As for the testing set, since those subjects were neither misclassified nor correctly classified, they were considered as 50% misclassified.

On the training set, cross-validation (CV) was used to estimate the optimal values of hyperparameters. In general, there is only one hyperparameter which is the cost parameter C of the linear C-SVM. In Voxel-STAND, there is a second parameter which is the threshold *t* of feature selection. In Voxel-COMPARE, a second parameter is the size σ of the Gaussian kernel and the third parameter is the number *n* of selected features. In Hippo-Volume, there is no hyperparameter. The optimal parameter values were determined using a grid-search and leave-one-out cross validation (LOOCV) on the training set. The grid search was performed over the ranges $C = 10^{-5}, 10^{-4.5}, ..., 10^{2.5}, 10^3, t = 0.06, 0.08, ..., 0.98, \sigma = 100, 200, ..., 1000 and <math>n = 1, 2, ..., 150$ (except for Voxel-COMPARE were $C = 10^0, 10^1, 10^{1.5}, 10^2, 10^{2.5}$).

For each approach, the optimized set of hyperparameters was then used to train the classifier using the training group; the performance of the resulting classifier was then evaluated on the testing set. In this way, we achieved unbiased estimates of the performances of each method.

For each method, we computed

• the number of true positives TP: the number of diseased individuals which were correctly identified by the classifier,

Classifier Method's name	Parzen Hippo-Volume-F	Parzen Hippo-Volume-S	Parzen Hippo-Shape	Linear SVM Voxel-Direct-D	Linear SVM Voxel-Direct-S	Linear SVM Voxel-Direct_VOI-I	Linear SVM Voxel-Direct_VOI-S	Linear SVM Voxel-Stand-D	Linear SVM Voxel-Stand-S	Linear SVM Voxel-Stand-Sc	Linear SVM Voxel-Atlas-D	Linear SVM Voxel-Atlas-S	Linear SVM Voxel-COMPARE-L	Gaussian SVM Voxel-COMPARE-S	Linear SVM Thickness-Direct	I inear SVM Thickness-Atlas	
	Pa	Pa	Pa	Lir	Lir	Lir	Lir	Lir	Lir	nplate Lir	Lir	Lir	Lir	Ga	Lir	Lir	-
Segmennanu leg	Freesurfer	SACHA	SACHA	DARTEL	SPM5	DARTEL	SPM5	DARTEL	SPM5	SPM5 custom ten	DARTEL	SPM5	DARTEL	SPM5	Freesurfer	Freesurfer	
Features	Volume	Volume	Shape	Direct	Direct	Direct VOI	Direct VOI	STAND-score	STAND-score	STAND-score	Atlas	Atlas	COMPARE	COMPARE	Direct	Atlas	
Category of method	Hippocampus			Voxel-based											Cortical thickness		

Table 5.2: Summary of the approaches in this study.

- the number of true negatives TN: the number of healthy individuals which were correctly identified by the classifier,
- the number of false positives FP: the number of healthy individuals which were not correctly identified by the classifier,
- the number of false negatives FN: the number of diseased individuals which were not correctly identified by the classifier.

We then computed

- the sensitivity defined as TP/(TP+FN),
- the specificity defined as TN/(TN+FP),
- the positive predictive value defined as PPV=TP/(TP+FP),
- the negative predictive value defined as NPV=TN/(TN+FN).

Finally, it should be noted that the number of subjects in each group is not the same. The classification accuracy does not enable to compare the performances between the different classification experiments. Thus we considered both the specificity and the sensitivity instead.

To assess whether each method performs significantly better than a random classifier, we used McNemar's chi square tests. Significance level was set at 0.05.

5.3 Results

The results of the classification experiments are represented in figure 5.1 for CN vs AD and in 5.2 for CN vs MCIc. Complete results are available in [Cuingnet et al., 2011]. For CN vs AD, all methods performed significantly better than chance (p < 0.05). Voxel-based and vertex-based methods reached high sensitivity and specificity. The hippocampus-based strategies were as specific but less sensitive: between 63% for Hippo-Volume and 69% for Hippo-Shape.

For CN vs MCIc, most methods were substantially less sensitive than for AD vs CN classification. All voxel-based and vertex-based methods except Voxel-COMPARE obtained significantly better results than a random classifier (p < 0.05). Methods based on hippocampal volume did not performed significantly better than chance while the method based on hippocampal shape was close to significance (p = 0.07). For MCInc vs MCIc, no method performed significantly better than a random classifier.

5.4 Discussion

A complete discussion of the comparison study can be found in [Cuingnet et al., 2011]. Here we focus on the discussion of the results of the methods based the hippocampus.



Figure 5.1: CN vs AD: classification results for the differents methods.



Figure 5.2: CN vs MCIc: classification results for the differents methods.

For both hippocampal volume and hippocampal shape, sensitivities and specificities were lower than those found in our previous studies on a different population (see previous chapter). This can be explained by several factors. First, ADNI is a multi-site database. This introduces variability in the MRI acquisitions, and also probably in the clinical diagnosis itself. Moreover the population included a large number of subjects with vascular lesions. As such, it probably represents a "less pure"AD population, with many subjects having a mixed pathology. Besides, the evaluation in our previous studied was carried out with a leave-one-out cross validation and not using completely separated training and testing sets. Moreover, this can also be due to that fact that all subjects were considered without taking into consideration the quality control of the hippocampus segmentation.

For CN vs AD, methods using the whole brain (or the whole cortex) reached substantially higher sensitivity than those based on the hippocampus. For the detection of prodromal AD, hippocampal-based approaches remained competitive with whole-brain methods. It thus seems that considering the whole brain is advantageous mostly at the most advanced stages. Indeed, at these more advanced stages, the atrophy is much more widespread. Moreover, as mentioned above, many subjects included in the ADNI have vascular lesions (white matter hyperintensities) which may be, at least partially, captured by whole brain methods and are obviously not modeled when considering only the hippocampus. In the future, it would be interesting to combine hippocampal analysis with methods assessing white matter hyperintensities [Samaille et al., 2012].



MORPHOMETRY OF A NEURO-PSYCHIATRIC DISEASE: GILLES DE LA TOURETTE SYNDROME

In this chapter, we present collaborative work with Yulia Worbe (neurologist at Pitié-Salpêtrière hospital and researcher within the team of Marie Vidailhet and Stéphane Lehéricy) on cortical and hippocampal morphometry in Gilles de la Tourette syndrome (GTS). GTS is a neurodevelopmental disorder characterized by tics that can be associated with psychiatric co-morbidities. GTS is a phenotypically heterogeneous syndrome in which symptoms may be restricted to simple tics, include complex tics and be associated with obsessive-compulsive disorders. In this study, we present evidence that the different clinical phenotypes of GTS are associated with distinct anatomical changes in the cortex and the hippocampus. These results support the hypothesis that different symptom dimensions in Gilles de la Tourette syndrome are associated with dysfunction of distinct brain areas.

This study was part of Yulia Worbe's PhD thesis. My specific contribution to that work was:

- statistical design and analysis with the random field theory for manifolds [Worsley et al., 1999]. This provided a unified statistical approach for the analysis of both cortical and hippocampal morphology. Our proposition to use this framework was decisive for the paper, by providing higher sensitivity and allowing detection of changes in the different clinical subgroups.
- analysis of hippocampal shape using spherical harmonics and point distribution models

This work was published in the following paper which is reproduced below: Y. Worbe, **E. Gerardin**, A. Hartmann, R. Valabregue, M. Chupin, L. Tremblay, M. Vidailhet, O. Colliot, S. Lehéricy, Distinct structural changes underpin the clinical phenotypes in adult patients with Gilles de la Tourette syndrome, *Brain*, 133(Pt 12):3649-60, 2010.

6. MORPHOMETRY OF A NEURO-PSYCHIATRIC DISEASE: GILLES DE LA TOURETTE SYNDROME

6.1 Abstract

Gilles de la Tourette syndrome is a childhood-onset neurodevelopmental disorder characterized by tics that are often associated with psychiatric co-morbidities. The clinical heterogeneity of Gilles de la Tourette syndrome has been attributed to the disturbance of functionally distinct cortico-striato-thalamo-cortical circuits, but this remains to be demonstrated. The aim of this study was to determine the structural correlates of the diversity of symptoms observed in Gilles de la Tourette syndrome. We examined 60 adult patients and 30 age- and gender-matched control subjects using cortical thickness measurement and 3 T high-resolution T1-weighted images. Patients were divided into three clinical subgroups: (i) simple tics; (ii) simple and complex tics and (iii) tics with associated obsessive-compulsive disorders. Patients with Gilles de la Tourette syndrome had reduced cortical thickness in motor, premotor, prefrontal and lateral orbito-frontal cortical areas. The severity of tics was assessed using the Yale Global Tic Severity Scale and correlated negatively with cortical thinning in these regions, as well as in parietal and temporal cortices. The pattern of cortical thinning differed among the clinical subgroups of patients. In patients with simple tics, cortical thinning was mostly found in primary motor regions. In patients with simple and complex tics, thinning extended into larger premotor, prefrontal and parietal regions. In patients with associated obsessive-compulsive disorders, there was a trend for reduced cortical thickness in the anterior cingulate cortex and hippocampal morphology was altered. In this clinical subgroup, scores on the Yale-Brown Obsessive-Compulsive Scale correlated negatively with cortical thickness in the anterior cingulate cortex and positively in medial premotor regions. These data support the hypothesis that different symptom dimensions in Gilles de la Tourette syndrome are associated with dysfunction of distinct cortical areas and have clear implications for the current neuroanatomical model of this syndrome.

6.2 Introduction

Gilles de la Tourette syndrome is a childhood-onset disorder characterized by the presence of multiple motor tics and at least one vocal tic for \geq 1 year [Association, 2000]. The expression of tics range from brief, recurrent and non-rhythmic motor or vocal actions (simple tics) to complex motor or vocal sequences (complex tics), such as touching behaviour or repetitive word pronunciation [Jankovic & Fahn, 1986]. The tics are often associated with psychiatric disorders such as obsessive-compulsive disorders, attention-deficit hyperactivity disorders and depression [Robertson, 2000]. Therefore, the phenotypic expression of Gilles de la Tourette syndrome is varied ranging from simple tics to a more complex association of tics and psychiatric co-morbidities. The pathophysiological origin of the clinical heterogeneity of Gilles de la Tourette syndrome is not yet fully understood. Inferences from various approaches support the hypothesis that Gilles de la Tourette syndrome is a neurodevelopmental disorder associated with dysfunction of cortico-striato-thalamo-cortical loops [Mink, 2003; Singer, 2005]. Cortical projections to the basal ganglia are functionally and topographically organized, leading to the concept of functional divisions of cortico-striato-thalamo-cortical loops into sensorimotor, associative and limbic circuits that are implicated in motor, cognitive and motivational aspects of behaviour, respectively [Alexander et al., 1986].

According to this model of basal ganglia organization, it was suggested that motor tics may result from the dysfunction of premotor and motor circuits, whereas behavioural disorders may result from the dysfunction of associative and limbic circuits [Singer, 2005]. This hypothesis is supported by several lines of evidence. In primate models, experiments showed that dysfunction of the premotor and sensorimotor circuits produced abnormal movements resembling simple motor tics [McCairn et al., 2009; Worbe et al., 2009], whereas dysfunction of the associative and limbic circuits resulted in behavioural disorders resembling complex tics and compulsions, respectively [Grabli et al., 2004; Worbe et al., 2009].

In patients with Gilles de la Tourette syndrome, studies have reported dysfunction of cortico-striato-thalamo-cortical circuits at different levels (Supplementary Table 1 summarizes the main results to date on structural and diffusion changes in Gilles de la Tourette syndrome). Dysfunction of paralimbic and sensory association areas were implicated in tic generation using functional MRI [Bohlhalter et al., 2006]. In the cortex, structural changes were observed in frontal, anterior cingulate, insular, parietal and temporal regions, using voxel-based techniques [Müller-Vahl et al., 2009], region of interest [Peterson et al., 2001] and cortical thickness measurements [Sowell et al., 2008; Fahim et al., 2010]. Structural changes were also reported in the striatum and globus pallidus [Peterson et al., 2003], the cerebellum [Tobe et al., 2009] using region of interest measurements, in the striatum [Ludolph et al., 2006] and the mid-brain [Garraux et al., 2006] using voxel-based techniques, as well as in the thalamus using diffusion imaging [Makki et al., 2009].

The severity of tics has been correlated with cortical thinning in the sensorimotor cortex and surrounding frontal and parietal areas [Sowell et al., 2008; Fahim et al., 2010], grey matter increase in the ventral putamen using voxel-based techniques [Ludolph et al., 2006] and diffusion orientation in the thalamus [Makki et al., 2008].

In contrast, the presence of psychiatric co-morbidities, such as obsessive-compulsive disorders and attention deficit hyperactivity disorder, correlated with volume reduction in the anterior caudate nucleus [Peterson et al., 2003; Bloch et al., 2005] and volume increase in the amygdala [Peterson et al., 2007]. Interestingly, volume of the hippocampus correlated both with severity of tics [Ludolph et al., 2006] and the presence of obsessive-compulsive disorders and attention deficit hyperactivity disorder [Peterson et al., 2007].

Overall, if results of previous studies provide support to the hypothesis that functionally distinct neuronal circuits are involved in tics and associated psychiatric co-morbidities, none of these studies directly addressed this question in clinical subgroups of patients. The purpose of this study was to determine the structural correlates of the diversity of symptoms observed in Gilles de la Tourette syndrome. We measured cortical thickness in clinical subgroups of adult patients with Gilles de la Tourette syndrome with simple tics, simple and complex tics and associated obsessive-compulsive disorders. We also examined structural changes in the hippocampus and their relationships with tics and obsessive-compulsive disorders.

6.3 Materials and methods

6.3.1 Subjects

Sixty adult patients with Gilles de la Tourette syndrome (mean age \pm SD: 30.3 \pm 10.8 years, 19 females) were enrolled in this study (Table 6.1). The inclusion criteria for the study were age > 18 years and confirmed diagnosis of Gilles de la Tourette syndrome. The exclusion criteria were age < 18 years, the presence of psychiatric disorders of Axe I established by the Mini International Neuropsychiatric Interview (French version) [Sheehan et al., 1998] including associated major depression, previous and actual history of psychosis, autistic spectrum disorders, substance abuse excluding tobacco, presence of other neurological or movement disorders except tics, contraindication to MRI examination and absence of informed consent.

Patients were selected from the 150 consecutive adult patients with Gilles de la Tourette syndrome from the database of the reference centre for Gilles de la Tourette syndrome in Paris on the basis of their medical history. Only 90 out of the 150 patients fulfilled the inclusion criteria. These subjects were contacted by the referent neurologists (Y.W. and A.H.) for diagnosis confirmation, medication status assessment and multidisciplinary consultation including neurological, neuropsychological and psychiatric evaluation. From these 90 patients, 16 were not included in the protocol for the following reasons:

- refusal to participate in the study;
- contraindication to MRI and
- the clinical course of Gilles de la Tourette syndrome was changed (i.e. symptoms too severe to perform MRI, presence of exclusion criteria).

Nine additional patients with actual history of attention deficit hyperactivity disorder were not included because their number was not sufficient to constitute a homogeneous group. Lastly, from the 65 patients who were included, five did not complete the MRI protocol for various reasons (claustrophobia, motion) and their data were excluded from the final analysis.

Severity of tics was assessed using the Yale Global Tic Severity Scale (YGTSS) [Leckman et al., 1989]. The presence and severity of associated obsessive-compulsive disorders was evaluated during the psychiatric consultation using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) assessment [Goodman et al., 1989]. The diagnosis of attention deficit hyperactivity disorder was established on the basis of Diagnostic and Statistical Manual-IV criteria of attention deficit hyperactivity disorder [Association, 2000]. In line with the purpose of the study, patients with Gilles de la Tourette syndrome were divided into three distinct clinical subgroups based on the clinical expression of their symptoms:

- patients with only simple motor and vocal tics (YGTSS complexity score of motor and vocal tics ≥2);
- patients with simple and complex motor and vocal tics (YGTSS complexity score of motor and vocal tics ≥2);

 patients with associated obsessive-compulsive disorders; these patients also presented simple and complex motor tics.

Six patients with Gilles de la Tourette syndrome presented obsessive-compulsive symptoms that did not fulfil the Diagnostic and Statistical Manual-IV-Text Revision criteria for obsessive-compulsive disorders, had no previous history of obsessive-compulsive disorders and were not previously treated for obsessive-compulsive disorders. These patients were included in the simple tics (n = 2) and complex tics (n = 4) groups.

Patients were compared with 30 age- and sex-matched healthy volunteers (29.1 ± 11) years, 11 females). The inclusion criteria for the study were age > 18 years and no history of neurological or psychiatric disorders. The exclusion criteria were the same as for the patients and previous history of tics (childhood tics). Patients and healthy volunteers gave written informed consent and the study was approved by the local ethics committee.

6.3.2 Magnetic resonance imaging acquisition

Images were acquired using a 3 T system (Siemens, TRIO 32 channel TIM system) with body coil excitation and 12-channel receive phased-array head coil. Anatomical scans were acquired using sagittal 3D T1-weighted magnetization prepared rapid acquisition gradient echo (inversion time: 900 ms, repetition time: 2300 ms, echo time: 4.18 ms, flip angle: 9°, partial Fourier 7/8, 1 average, voxel size: $1 \times 1 \times 1$ mm³). All patients included in the study were asked to suppress their tics during image acquisition to avoid movement artefacts.

6.3.3 Cortical thickness measurements

Cortical thickness measurements were performed with the FreeSurfer image analysis suite (Massachusetts General Hospital, Boston, MA, USA), which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of this procedure are described in previous publications [Dale et al., 1999; Fischl et al., 1999a,b]. Briefly, the processing included motion correction and averaging of multiple volumetric T1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, intensity normalization, tessellation of the grey matter-white matter boundary, automated topology correction and surface deformation following intensity gradients to optimally place the grey matter-white matter and grey matter-cerebrospinal fluid borders at the location where the greatest shift in intensity defined the transition to the other tissue class. Cortical thickness was then calculated as the closest distance from the grey matter-white matter boundary to the grey matter-cerebrospinal fluid boundary at each vertex on the tessellated surface [Fischl & Dale, 2000]. All cortical thickness maps were then registered onto the common template provided with FreeSurfer. As cortical thickness varies with gender and age [Sowell et al., 2007], these variables were included as covariates in all statistical comparisons to exclude the effect of gender and age from the observed structural differences.

6.3.4 Hippocampal morphometry

Hippocampal morphometry was performed on 57 patients with Gilles de la Tourette syndrome and 28 controls; 3 patients and 2 controls were excluded from the study due to abnormal hippocampal shape that may have altered the morphometry analyses (large hippocampal malrotation [Bernasconi et al., 2005]).

The hippocampi were segmented from the T1-weighted images using the fully automatic method Segmentation Automatique Compétitive de l'Hippocampe et de l'Amygdale [Chupin et al., 2009a]. This approach allowed the simultaneous segmentation of both the hippocampus and the amygdala based on competitive region growing. It included prior knowledge of the location of the hippocampus and the amygdala derived from a probabilistic atlas, and of the relative positions of these structures with respect to anatomical landmarks, which were automatically identified. This method has been validated by comparison with manual tracing in young healthy participants and patients with Alzheimer's disease and has proved to be reliable, fast and accurate [Chupin et al., 2009a].

To investigate the specific contribution of local changes within the hippocampus, we performed a statistical 3D surface-based shape analysis relying on the spherical harmonics approach [Styner et al., 2004].

The analysis was performed using the SPHARM-PDM software developed by the University of North Carolina and the National Alliance for Medical Imaging Computing (http:// www.namic.org/Wiki/index.php/Algorithm:UNC:Shape_Analysis). SPHARM is a mathematical approach, representing surfaces with spherical topology, which can be seen as a 3D analogue of Fourier series expansion. It has been successfully used to analyse hippocampal shape differences in a variety of neurological and psychiatric conditions including Alzheimer's disease [Gerardin et al., 2009], schizophrenia [Styner et al., 2004] and bipolar disorder [Hwang et al., 2006]. In brief, the SPHARM approach took the following steps. First, hippocampal segmentations were converted to surface meshes and a spherical parameterization was computed, creating a one-to-one map between each point on the surface and each point on a sphere. The surface was expanded into a series of spherical harmonics. The coefficients of the series expansion were normalized in order to eliminate effects of rotation, translation and scale. The SPHARM representation was transformed into a triangulated surface (called the SPHARM-PDM), based on a uniform subdivision of the spherical parameterization. The SPHARM-PDM was finally spatially aligned using rigid Procustes alignment, giving a one-to-one mapping between points of each hippocampus.

6.3.5 Statistical analyses

Surface-based analyses of both cortical thickness and hippocampal shape were performed using Surfstat software (http://www.math.mcgill.ca/keith/surfstat/).

Cortical thickness maps were smoothed using a 20 mm surface-based kernel. The comparison of cortical thickness between groups was carried out using a univariate linear model at each vertex. For the comparison of hippocampal shape between groups, we used the Hotelling T^2 metric to test for group differences in the spatial location (x,y,z) at each vertex of the hippocampal surface [Styner et al., 2006]. In all analyses, statistics were corrected for multiple comparisons using the random field theory for non-isotropic images [Worsley

et al., 1999]. A statistical threshold of p < 0.005 was first applied (height threshold). An extent threshold of p < 0.05 corrected for multiple comparisons was then applied at the cluster level unless stated otherwise. Differences obtained using lower thresholds are reported as trends.

All clinical variables were compared using SigmaStat software and one way ANOVA statistics.

6.4 Results

6.4.1 Clinical subgroups of patients with Gilles de la Tourette syndrome

The clinical characteristics and medication of the patients are presented in Table 6.1. The simple tics group was characterized by the presence of simple motor tics of the face (mostly eye blinks), neck and hands and simple vocal tics (throat noises). The mean \pm SD YGTSS complex tics score was 0.6 \pm 1.1.

The complex tics group included patients with simple and complex motor and vocal tics-mostly complex motor tics of the hand, touching behaviour, echo-, copro- and paliphenomena. The mean YGTSS complex tics score was 4.0 ± 2.0 .

The GTS patients with associated obsessive-compulsive disorders group included patients with simple and complex tics and associated obsessive-compulsive disorders (checking and washing compulsions). The mean YGTSS complex tics score was 1.9 ± 1.6 .

The complex tics group differed from the simple tics and obsessive-compulsive disorders groups by the presence of higher numbers of tics (p = 0.009) and greater complexity YGTSS scores (p < 0.001). There were no statistically significant differences between all three groups in frequency (p = 0.1), intensity (p = 0.2) and interference (p = 0.09) YGTSS sub-scores. The mean Y-BOCS score was significantly higher in the obsessive-compulsive disorders group (Y-BOCS score: 12.8±6.0, p < 0.001) than in the other two groups (simple tics: 1.8±0.5, complex tics: 1.7±0.8).

6.4.2 Cortical thickness in all patients with Gilles de la Tourette syndrome

In all patients with Gilles de la Tourette syndrome compared with controls (Figure 6.1, the cortical areas of diminished thickness included the motor cortex, the postero-lateral part of the superior frontal gyrus [corresponding to Brodmann area (BA) 6], the posterior part of the middle frontal gyrus (BA 6, 8 and 9) in the left hemisphere, and the inferior frontal gyrus (BA 45) and the lateral part of the orbito-frontal gyrus (BA 47) in the right hemisphere. Cortical thickness changes in patients with Gilles de la Tourette syndrome were not modified by age (see online Supplementary data). There was no difference in cortical thickness between males and females with Gilles de la Tourette syndrome matched for age, YGTSS severity and disease duration (Supplementary data).

Table 6.1: Clinical characteristics and medication of Gilles de la Tourette syndrome

Number of patients Males	group 21 14	group 22 16	12 12 12 12
Female	7	8	4
Age (years)	29 ± 10	30 ± 13	32±9
Age at onset (years)	$6.3{\pm}1.0$	7.3 ± 2.1	6.5 ± 1.3
Mean syndrome duration (years)	23.0 ± 9.5	23.0 ± 12.7	25.5 ± 8.7
Premonitory urges (% of patients)	28.6	31.2	12.0
YGTSS/50	$14.1 {\pm} 6.4$	$21.4 {\pm} 6.8$	15.9 ± 5.9
YGTSS sub-scores			
Number of tics	$2.9 {\pm} 1.0$	$4.0{\pm}1.3$	2.9 ± 0.8
Frequency of tics	$3.9{\pm}1.5$	$4.8 {\pm} 1.6$	4.0 ± 1.6
Complexity of tics	$0.6{\pm}1.1$	$4.0{\pm}2.0$	$1.9{\pm}1.6$
Interference of tics	$2.9 {\pm} 1.0$	$1.7 {\pm} 3.8 {\pm} 1.7$	2.8 ± 1.4
Intensity of tics	$3.8{\pm}1.9$	$4.7 {\pm} 1.7$	4.2 ± 1.7
Y-BOCS/40	$1.8 {\pm} 0.5$	$1.7 {\pm} 0.8$	$12.8 {\pm} 6.0$
Treatment (% of patients)			
Non-treated	66.7	30.4	43.8
Neuroleptics	23.8	56.5	43.8
Benzodiazepines	9.5	4.3	12.5
Anti-depressants	4.8	13.0	25.0

6. Morphometry of a neuro-psychiatric disease: Gilles De La Tourette Syndrome



Figure 6.1: Regions of cortical thinning in all patients with Gilles de la Tourette syndrome (GTS) compared with controls. Clusters are significant at p < 0.005 corrected for multiple comparisons. L=left hemisphere; R=right hemisphere

6.4.3 Cortical thickness in clinical subgroups of patients with Gilles de la Tourette syndrome

Group comparison of cortical thickness showed distinct patterns of cortical alteration in the clinical subgroups of patients. In the simple tics group compared with controls, there was diminished cortical thickness in the posterior part of the left middle frontal gyrus-premotor cortex (BA6) and the left motor cortex in the region of the representation of the upper and lower limbs and the upper part of the face area (Figure 6.2).

In the complex tics group compared with controls, the cortical areas of diminished thickness included the posterior parts of the middle and inferior frontal gyrus (corresponding to BA 6, 8, 9, 44 and 46), the ventral and lateral parts of the left motor cortex in the region of the face area and the corresponding part of the primary sensory cortex, the anterior and inferior parietal cortex (BA 39 and 40) in the left hemisphere, as well as the right inferior frontal gyrus (BA 45) and the lateral part of the right orbito-frontal gyrus (BA 47) (Figure 6.2).

Lastly, in Gilles de la Tourette patients with associated obsessive-compulsive disorders group (Figure 6.3), there were no significant differences at < 0.005 corrected for multiple comparisons. However, there was a trend for cortical thinning in the left ventral anterior cingulate cortex (BA 32) as well as in small areas of the left middle frontal gyrus (BA 8/9), the left motor cortex (BA 4) and the superior parietal lobule (BA 7), bilateral occipital lobes (BA 19/37) and posterior parts of right orbito-frontal gyrus (BA 47) (p < 0.005 uncorrected for multiple comparisons). There were no regions of cortical thickening in any of the Gilles de la Tourette syndrome groups compared with controls.

6. MORPHOMETRY OF A NEURO-PSYCHIATRIC DISEASE: GILLES DE LA TOURETTE SYNDROME



Figure 6.2: Region of cortical thinning in clinical subgroups with Gilles de la Tourette syndrome compared with controls. (A) Patients with simple tics (GTS-TS). (B) Patients with Gilles de la Tourette syndrome with simple and complex tics (GTS-TC). Clusters are significant at p < 0.005 corrected for multiple comparisons. L=left hemisphere; R=right hemisphere.

6.4.4 Hippocampal volumes and morphology in clinical subgroups of patients with Gilles de la Tourette syndrome

In all patients with Gilles de la Tourette syndrome compared with controls, there was a 3.0% reduction in hippocampal volume. The clinical subgroups analysis showed that this reduction was only significant in Gilles de la Tourette patients with associated obsessive- compulsive disorders group (3.5%, p = 0.03), mostly in the right hippocampus (4.4%). The hippocampal volume was only slightly diminished in the other groups and the difference was not significant (simple tics: 2.9%, complex tics: 2.7%, both p-values = 0.12). The morphological analysis of the hippocampus showed significant changes in the obsessive-compulsive disorders group only. In this group, the morphology of the postero-lateral part of the right hippocampus differed significantly from the morphology of the healthy volunteers (Figure 6.3).

6.4.5 Correlations between YGTSS and Y-BOCS scores and cortical thickness in patients with Gilles de la Tourette syndrome

The correlation between the YGTSS scores (YGTSS/50) and cortical thickness in patients with Gilles de la Tourette syndrome is presented in Figure 6.4. In all patients with Gilles de la Tourette syndrome, the YGTSS scores correlated negatively with cortical thickness in the posterior part of the medial orbital gyrus (BA 13), the posterior part of the inferior frontal



Figure 6.3: Structural changes in patients with Gilles de la Tourette syndrome with associated obsessive-compulsive disorder (GTS-OCD) compared with controls. (A)Regions of cortical thinning in patients compared with controls, p < 0.005 uncorrected for multiple comparisons. (B) Structural changes in the hippocampus in patients. *Left*: medial view; *right*: lateral view of hippocampus. Clusters are significant at p < 0.005 corrected for multiple comparisons. L=left hemisphere; R=right hemisphere.

gyrus (BA 44) and the ventral part of the primary sensorimotor cortex in the region of the face area and adjacent premotor cortex in the left hemisphere, the antero-medial temporal lobe (BA 34, 35 and 28) and the temporal pole (BA 38) in the right hemisphere, and bilaterally in lateral parts of the orbito-frontal and inferior frontal gyri (BA 47), the operculum, the superior (BA 22, 41 and 42) and middle (BA 21) temporal gyri and inferior regions of the parietal lobe (BA 40). No regions showed a positive correlation with YGTSS. There was no significant correlation between cortical thickness and Y-BOCS scores at the corrected threshold of p < 0.005. Given our hypothesis of a relation between obsessive-compulsive disorders and structural changes in limbic regions, we looked for correlations in the Gilles de la Tourette patients with associated obsessive-compulsive disorders group at a lower statistical threshold of p < 0.05. Using this threshold in this group, there was a negative correlation between increased Y-BOCS scores and reduced cortical thickness in the left dorsal and ventral anterior cingulate cortex (BA 32 and 24) and small areas of the occipital cortex (right BA 18 and left BA 19) (T score = 2, Figure 6.5). There was also a positive correlation between increased Y-BOCS score and increased cortical thickness bilaterally in the medial part of the superior frontal gyrus including the supplementary motor area (BA 6), the anteromedial part of the superior frontal gyrus (BA 8 and 9), the inferior temporal gyrus (BA 21) and the medial temporo-occipital gyrus (BA 35 and 36) in the left hemisphere, and in posterior parts of the superior and middle frontal gyri (ventral parts of BA 6 and 8), the anterior parts of the middle frontal gyrus (BA 46), the posterior part of the gyrus rectus (BA 14) and the inferior



YGTSS negative correlation in all GTS patients

Figure 6.4: Cortical regions negatively correlated with the YGTSS score in all patients with Gilles de la Tourette syndrome. Clusters are significant at p < 0.005 corrected for multiple comparisons. L=left hemisphere; R=right hemisphere.



Figure 6.5: Y-BOCS score correlations in the Gilles de la Tourette patients with associated obsessive compulsive disorders (GTS-OCD). A: Cortical regions with negative correlation. B: Cortical regions with positive correlation; p < 0.05 uncorrected for multiple comparisons. L=left hemisphere; R=right hemisphere.

part of the primary motor cortex, corresponding to the face area in the right hemisphere (*T* score = 2, Figure 6.5).

6.5 Discussion

We provide evidence that the different phenotypic expressions in Gilles de la Tourette syndrome are due to dysfunction of different cortical areas. Simple tics were associated with cortical thinning in premotor and sensorimotor areas and complex tics with cortical thinning in larger premotor, prefrontal and parietal associative areas. The presence of obsessivecompulsive disorders was associated with altered hippocampal morphology and with cortical thinning of the anterior cingulate cortex. Severity of tics correlated negatively with cortical thinning in frontal, parietal and temporal regions, whereas the severity of obsessivecompulsive disorders correlated negatively with cortical thickness in the anterior cingulate area and positively in prefrontal regions.

6.5.1 Cortical thickness in patients with Gilles de la Tourette syndrome compared with controls

Adult patients with Gilles de la Tourette syndrome presented important thinning in the left motor, premotor and dorso-lateral prefrontal regions and the right ventro-lateral and lateral orbitofrontal areas. Cortical thinning in all these regions has been reported in children [Sowell et al., 2008] and young adults [Fahim et al., 2010] with Gilles de la Tourette syndrome in previous studies. Using diffusion MRI, changes were also observed in the white matter of the sensorimotor regions and in fronto-striatal circuits in children [Makki et al., 2009] and adults [Thomalla et al., 2009] with Gilles de la Tourette syndrome. Taken together, these data pointed to a global dysfunction of grey and white matter components of cortical projections to the striatum in Gilles de la Tourette syndrome.

Cortical changes clearly predominated in the left hemisphere. A similar predominance of cortical thinning in left motor regions has already been reported in young adults with Gilles de la Tourette syndrome [Fahim et al., 2010] but not in children with Gilles de la Tourette syndrome [Sowell et al., 2008]. The left-sided predominance of structural changes in adults may be related to the asymmetry of cortical areas consequent to brain maturation as shown using structural imaging [Kloppel et al., 2010], diffusion connectivity [Iturria-Medina et al., 2011] or functional MRIé[Woolley et al., 2010]. In contrast, regional volumetric [Petersen et al., 2001] and voxel-based morphometry studies [Müller-Vahl et al., 2009] did not report any asymmetry in adult patients with Gilles de la Tourette syndrome. Further studies are therefore needed to investigate the asymmetry of structural changes in Gilles de la Tourette syndrome.
6.5.2 Different patterns of cortical thinning in clinical subgroups of patients with Gilles de la Tourette syndrome

Simple and complex tics differed in their phenomenological expression and are thought to represent biologically relevant symptom subclasses [Mathews et al., 2007; Robertson, 2000]. In contrast to the basic motor patterns of simple tics, complex tics are characterized by complex sequential motor or vocal patterns such as touching behaviour, repetitive word pronunciation or motor action or vocal imitations [Jankovic & Fahn, 1986]. Our data suggest that these clinical differences are underlain by different structural changes. The simple tics were associated with structural changes in primary motor and adjacent premotor regions. In the simple tics group, cortical thinning was found in the primary motor area of the face and hand, which fits well with the orofacial and hand predominance of the tics. Cortical thinning in these regions was also observed in the two other groups who also presented simple tics, although thinning was less marked in the obsessive-compulsive disorders group.

The complex tics group was characterized by cortical thinning in larger frontal and parietal regions. Previous studies have shown that these regions were recruited during movements of increasing complexity [Catalan et al., 1998; Lehéricy et al., 2006] as well as in the learning of new motor sequences [Lehéricy et al., 2005; Doyon et al., 2009]. The dysfunction of these regions may therefore be necessary for the production of complex tics. Thinning of the ventrolateral premotor and prefrontal regions (BA 44) was also specific to the complex tics group. These regions and the inferior parietal cortex are part of the mirror neuron system, which is implicated in movement imitation [Molenberghs et al., 2009]. Dysfunction of this network may therefore be associated with the imitation behaviour frequently observed in patients with complex tics. Alternatively, the larger structural changes observed in the complex tics group may be related to the greater severity of the syndrome in this group. Indeed, the complex tics group had a greater tics score on the YGTSS than the two other groups. However, this was mostly due to the larger number of complex tics. This suggests that even if severity differed between the groups of patients, it was mainly driven by complexity of the tics in the complex tics group.

The association of tics with obsessive-compulsive disorders was characterized by reduced volume and altered morphology of the hippocampus, in agreement with previous volumetric [Peterson et al., 2007] and voxel-based morphometry [Ludolph et al., 2006] studies in children and adults with Gilles de la Tourette syndrome with associated obsessivecompulsive disorders, as well as in patients with obsessive-compulsive disorders without tics [Hong et al., 2007; Atmaca et al., 2008].

In the Gilles de la Tourette patients with associated obsessive-compulsive disorders, there was a trend for diminished cortical thickness in the ventral anterior cingulate cortex as well as in regions associated with tics in the other Gilles de la Tourette syndrome groups. The smaller number of patients included in this group may explain why differences were not detected using the corrected threshold. Reduced cortical thickness in the anterior cingulate cortex was specific to the Gilles de la Tourette patients with associated obsessive-compulsive disorders group and was not observed in the two other groups even using the uncorrected threshold. This finding was in line with the reduced volume of the anterior cingulate cortex showed in adolescent and adult patients with obsessive-compulsive disorders without tics [Radua &

Mataix-Cols, 2009; Rotge et al., 2009]. In children with Gilles de la Tourette syndrome, positive correlation was also reported between obsessive-compulsive disorders and connectivity scores between the subcallosal gyrus and the lentiform nucleus using diffusion imaging [Makki et al., 2009].

The anterior cingulate cortex and the hippocampus are functionally heterogeneous structures, which are part of the limbic system [Paus et al., 2001; Fanselow & Dong, 2010]. The ventral part of the anterior cingulate cortex is implicated in the assessment and regulation of emotional information and anxiety [Paus et al., 2001]. The hippocampus is involved in the regulation of aversive emotional states (mostly fear and anxiety) as well as in emotionally driven memorization and conditioning [Fanselow & Dong, 2010]. Consequently, both structures may mediate the expression of anxiety observed in obsessive-compulsive disorders.

6.5.3 Cortical structural changes correlated with the YGTSS and the Y-BOCS

Severity of tics measured with the YGTSS correlated negatively with cortical thickness in all regions that were affected in the group comparison, in agreement with previous studies [Sowell et al., 2008; Fahim et al., 2010].

Severity of tics also correlated with cortical thickness in the temporal, ventro-lateral prefrontal and adjacent orbito-frontal cortices.

Positron emission tomography [Stern et al., 2000] and functional MRI studies [Peterson et al., 1998; Mazzone et al., 2010] reported abnormal activity in temporal regions in patients with Gilles de la Tourette syndrome, suggesting that they are implicated in the control of tics. Similarly, surgical ablation of the temporal cortex in patients with Gilles de la Tourette syndrome with co-occurring epilepsy resulted in the exacerbation of tics [Chemali & Bromfield, 2003; Sinno et al., 2006]. In addition,functional MRI studies showed that the ventro-lateral prefrontal and the lateral orbital cortex are implicated in motor response inhibition and behavioural persistence [Gusnard et al., 2003; Aron et al., 2007]. The dysfunction of these regions thus may contribute to the deficient motor control and tic persistence.

The severity of obsessive-compulsive disorders, measured using the Y-BOCS scale had a tendency to correlate negatively with thinning in the left ventral and dorsal anterior cingulate cortex. The left anterior cortex is functionally lateralized [Lutcke & Frahm, 2008] and plays an important role in error detection [Paus et al., 2001; Swick & Turken, 2002]. The cognitive model [Salkovskis, 1985] and functional MRI studies [Fitzgerald et al., 2005] indicate that altered error detection is one of the pathological mechanisms of obsessive-compulsive disorders. Accordingly, thinning of the dorsal anterior cingulate cortex fits well with more severe obsessive-compulsive disorder symptoms in patients with Gilles de la Tourette syndrome.

Less severe obsessive-compulsive disorder symptoms correlated areas (mostly the supplementary motor area) were involved in sel f performance evaluation, in the initiation and inhibitory control of actions and in cognition [Aron et al., 2007; Passingham et al., 2010]. The fact that these regions correlate with less severe obsessive-compulsive disorder symptoms suggests that they contribute to the cognitive control of obsessive-compulsive disorders.

6.5.4 Brain correlates of cortical thinning

The structural changes may be primary and caused by the underlying cause of the disease. Recent neuropathological studies in Gilles de la Tourette syndrome showed both decreased number and deviant distribution of basal ganglia inhibitory interneurons [Kalanithi et al., 2005; Kataoka et al., 2009]. As cortical and basal ganglia interneurons originate from the same structures during brain development [Wonders & Anderson, 2006] reduced number of inhibitory interneurons may also be present in the cortex, leading to both structural changes and functional abnormalities. This suggestion is in line with neurophysiologicalé[Orth & Rothwell, 2009; Heise et al., 2010] and functional MRI data [Bohlhalter et al., 2006], which showed diminished intracortical inhibition and hyperactivity of premotor and sensorimotor cortex in Gilles de la Tourette syndrome. Therefore, thinning of cortical regions fits well with the developmental hypothesis of Gilles de la Tourette syndrome.

6.6 Limitations

A limitation of this study was the inclusion of patients with different medications. The impact of neuroleptic medication on brain structural changes is controversial, as studies have reported either no impact [Peterson et al., 2001] or changes in brain volume [Scherk & Falkai, 2006]. The variation of cortical thickness was not influenced by neuroleptic medication in cross-sectional studies of patients with schizophrenia that typically used a higher dosage of neuroleptics [Kuperberg et al., 2003; Narr et al., 2005]. Consequently, the different patterns of cortical changes in our study were most probably related to symptom expression and not to differences in medication. In addition, neuroleptics may influence tic measurement using the Y-BOCS. Correlation data may thus be influenced by the medication status. Lastly, correlation data should be considered with caution as structural changes could reflect either the causes or the consequences of the symptoms.

6.7 Conclusion

The present study shows that cortical areas are variably involved in Gilles de la Tourette syndrome, a finding that provides an explanation for the clinical heterogeneity of the disorder. Combined with experimental results obtained in the basal ganglia in primates [Grabli et al., 2004; Worbe et al., 2009], this suggests that dysfunction of specific cortical-basal ganglia circuits lead to the clinical heterogeneity of Gilles de la Tourette syndrome symptoms.

PART 3

ULTRA HIGH FIELD MRI



BUILDING AN ATLAS OF HIPPOCAMPAL INTERNAL STRUCTURE FROM POST-MORTEM MRI

Ultra-high field MRI (7T and higher) provides new contrasts and increased spatial resolution, making it possible to visualize the complex anatomy of hippocampal subregions. A prerequisite to shape analysis is to be able to reliably delineate hippocampal subregions. In this chapter, we thus propose a new manual protocol to segment the subregions of the hippocampus from very high resolution MR images.

Besides, it would be particularly interesting to have a 3D digital atlas of hippocampal subregions, if possible with isotropic resolution. In the context of this thesis, a 3D atlas is going to be very valuable to validate the shape analysis approach presented in the next chapters. Beyond the validation of shape analysis approaches, such an atlas would be useful for designing automatic segmentation procedures or for analyzing functional images for instance. In this chapter, we applied the proposed segmentation protocol to postmortem hippocampal specimens (acquired at University of Pennsylvania and available on the internet [Yushkevich et al., 2009]), to build a 3D atlas of hippocampal subregions.

7.1 Background

Quantitative study of hippocampal morphology requires its segmentation and thus the definition of a segmentation protocol. Quite a large number of manual segmentation protocols of hippocampus from conventional T1-weighted MR images have been proposed [Jack et al., 1995; Hasboun et al., 1996; Pantel et al., 2000]. Although manual delineation can be seen as a gold standard, different MRI parameters may contribute to a wide variability of volume estimates as pointed out in [Geuze et al., 2004]. Moreover, the large number of different anatomical protocols for defining the hippocampal boundaries may contribute to inconsistencies and may thus prevent the comparison of similar studies. [Konrad et al., 2009]

7. BUILDING AN ATLAS OF HIPPOCAMPAL INTERNAL STRUCTURE FROM POST-MORTEM MRI



Figure 7.1: The left figure illustrates the marking scheme used in [Mueller et al., 2007]. The scheme was based on anatomical landmarks. The following figures show a typical example of hippocampal subfield segmentation, from the most anterior slice to the most posterior slice. From [Mueller et al., 2007]

reviewed the existing anatomical protocols for delineating the hippocampus in MR images, and identified five major areas where variations between protocols occur. In [Frisoni & Jack, 2011], the authors selected the 12 most used hippocampal segmentation protocols from the Alzheimer's literature and extracted the differences among these protocols, in order to create a standard and shared protocol.

However, using conventional MRI, only the external border of the hippocampus is visible and all these protocols thus treat the hippocampus as a single entity. As seen in chapter 2, the internal anatomy of the hippocampus is particularly rich, and presents as a complex combination of subfields. These subfields are defined by the type of cell types they contain, as seen in section 2.4, have distinct functions and can be preferentially affected by different diseases. To understand the individual role of these regions in either structural or functional studies, it is necessary to isolate these regions with a validated procedure.

Recent developments in high resolution imaging, in particular using ultra-high field MRI (7T and higher), have made it possible to visualize the internal structure of the hippocampal formation with a high level of detail, and have made possible the differentiation between the subfields. Thus, new segmentation protocols for delineating hippocampal subregions were recently proposed [Mueller et al., 2007; Van Leemput et al., 2009], providing the opportunity to extend the volumetric or morphometric study at the level of the subfields. Using T2-weighted sequences with 0.4x0.5x2mm resolution at 4T, [Mueller et al., 2007] proposed a protocol to segment the subiculum, CA1, CA2 and CA3/4 and the dentate gyrus. The resulting segmentation is illustrated on figure 7.1. However, their approach involves the definition of many arbitrary landmarks. Moreover, using 2 mm thick slices prevents from building a 3D model. Using T1-weighted sequences with 0.4x0.4x0.8 mm at 3T, [Van Leemput et al., 2009] proposed an automated procedure to segment fimbria, presubiculum, subiculum, CA1, CA2/3, and CA4/DG, using an atlas based on manual segmentations. The resulting segmentation is illustrated on figure 7.2. Again, several user-defined landmarks are included in the protocol.

[Yushkevich et al., 2009] acquired ultra high resolution images of postmortem hippocampal specimens using a 9.4 Tesla MRI for small animals, in order to build an atlas of hip-



Figure 7.2: From left to right: cross-sectional slices of an ultra-high resolution MRI scan, manual delineation of the hippocampal subfields and corresponding automated segmentation. From [Van Leemput et al., 2009]

pocampal substructure. The main subfields of the hippocampus (cornu ammonis fields CA1, CA2/3; the dentate gyrus; and the vestigial hippocampal sulcus) were labeled in the images manually. The MR images and the corresponding segmentations are available online (http://www.nitrc.org/projects/pennhippoatlas/). These quasi-isotropic segmentations are potentially very interesting for studying the internal morphology of the hippocampus. However, as can be seen on figure 7.3, the topology of Ammon's horn is not correct and its convolutions are not adequately segmented, which prevents from using this segmentation for shape analysis. Thus, we propose in section 7.2 a segmentation protocol carefully designed to delineate the different subparts of the hippocampal formation.

7.2 Segmentation of hippocampal subregions

In this chapter, we first propose a protocol to manually delineate hippocampal subregions from very high resolution MR images. The protocol was defined conjointly with Marie Chupin and Dominique Hasboun. We then apply this protocol to create a 3D atlas by segmenting one of the postmortem specimens acquired at 9.4T by [Yushkevich et al., 2009].

Some examples of images used for the segmentation are shown in figure 7.4. These images come from both ex-vivo and in-vivo acquisitions. The ex-vivo images are part of the aforementioned acquisisitions performed by [Yushkevich et al., 2009]. The in-vivo MRI were acquired as part of our collaboration with the University of Minnesota. The hippocampal

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Figure 7.3: Coronal slices of the MR images of the hippocampus, and segmentation presented in [Yushkevich et al., 2009]. The first row is a slice of the hippocampal tail, the second a slice of the body, the three last are slices of the head. Dark blue: CA1; Light blue: CA2-CA3.; Red: Stratum radiatum-lacunosum-moleculare of the cornu Ammonis and vestigial hippocampal sulcus; Yellow: stratum moleculare of the gyrus dentatus; Green: hilum of the gyrus dentatus. As can be seen from these slices, the segmentation does not respect the convolutions of Ammon's horn and the topology of the regions is not correct.

formation is visible in coronal, sagittal and axial planes. White matter corresponds to dark voxels, gray matter corresponds to lighter voxels.

7.3 Basic principles of segmentation

We won't give here a complete description of the procedure, but rather present the main guidelines of the protocol. In this protocol, the main subregions of the hippocampal formation (cornu Ammonis fields, the dentate gyrus and the subiculum) are manually labeled in the images using a combination of intensity and geometrical information. The reader is invited to refer to the chapter 2 for a definition of the anatomical terms. The segmentation is done in the coronal plane and the tri-dimensional coherence is ensured by checking the axial and the sagittal planes, unless otherwise stated.

7.3.1 Identification of the head, the body and the tail

The first step of the protocol is to identify the limits of the body, the head and the tail.

The easiest limit to identify is certainly the most anterior part of the body: it corresponds to the first slice where the median part of the uncus is no longer visible. This limit can be confirmed in the sagital plane. This first slice can be seen in figure 7.5, highlighted in red.

The identification of the most posterior slice of the body is mainly based on a geometric feature. Indeed, the change of orientation of the main axis of the hippocampus defines the end of the body; after this change of orientation, the Cornu Ammonis and the gyrus dentatus begin to lose their usual C-shaped configuration in coronal planes, and the fimbria, at the superior-medial aspect of the hippocampus, enlarges and takes a "fan" shape. The change of orientation can also be located on sagittal planes. These modifications can be seen in figure 7.6.

Another limit that can be easily identified is the anterior limit of the hippocampus, the beginning of the head. The head is anteriorly recovered by the alveus, thus the first slice of the head is marked by the apparition of gray matter "inside" the white matter. This is shown on figure 7.7.

At last, the most difficult limit is certainly the posterior limit of the hippocampus, the end of the tail. This limit is detected by the apparition of the shape of a usual sulcus. Indeed, Cornu Ammonis, in the anterior part of the tail, has a similar configuration to that of the body. Progressively, Cornu Ammonis presents dentes of decreasing size, and small protrusions of the gyrus dentatus are still visible. In the posterior part of the tail, Cornu Ammonis becomes smooth and narrow, until it takes the shape of a "classical"gyrus.

We manually delineate the different segments of the hippocampus in a specific order.

- We begin by segmenting the body, from the most anterior to the most posterior slice.
- Then we come back to segment the head, in the inverse order. Indeed, it is easier to segment the head by taking into account the manual delineation of the body in the posterior part of the head, before the apparition of the digitations.
- At last, we segment the head, from the anterior to the posterior slice.

7. BUILDING AN ATLAS OF HIPPOCAMPAL INTERNAL STRUCTURE FROM POST-MORTEM MRI



Figure 7.4: Coronal, sagittal and axial sections of the hippocampal formation. **Top**: 9.4T MRI of a post-mortem hippocampus sample. Ex-vivo acquisition, voxel size = 0.30x0.20x0.20 mm. More details can be found in [Yushkevich et al., 2009]. **Bottom**: 7T MRI of an hippocampus. In-vivo acquisition, voxel size = 0.25x0.25x1 mm.



Figure 7.5: Identification of the most anterior slice of the body. These are four consecutive slices of a high-resolution ex-vivo image. The left slice is the last slice of the head: a small part of the uncus is visible at the level of the red arrow. The next slice corresponds to the anterior limit of the body: the uncus disappeared, and the characteristic C-shape of the hippocampal body is clearly identifiable.



Figure 7.6: Identification of the most posterior part of the body, highlighted in red. In the left figure, we recognize the characteristic shape of the hippocampal body, and the fimbria, which appears hypointense and has been marked with the red arrow, remains thin. The middle figure, represents the end of the body: in the next figure, one can see the enlargement of the fimbria due to the change of orientation of the main axis. This is a landmark for the anterior limit of the tail.

7. BUILDING AN ATLAS OF HIPPOCAMPAL INTERNAL STRUCTURE FROM POST-MORTEM MRI



Figure 7.7: Anterior limit of the hippocampus, highlighted in red. In the left figure, only white matter is visible at the level of the red arrow. At the same level in the middle figure, an "island" of gray matter appears inside the white matter. In the last figure, we can clearly distinguish the Cornu Ammonis under the alveus.



Figure 7.8: The different segments of the hippocampus are segmented in a specific order. First the body, then the head, and finally the tail

The subfield segmentations are reviewed and corrected for each segment, as necessary to satisfy the protocol. These steps are illustrated on figure 7.8

7.3.2 Segmentation of subfields

The segmentation is performed by taking into account the intensity information in the image as much as possible. In the body, it is thus possible to distinguish clearly :

- strata with the densest cell bodies (stratum pyramidale) of CA1, CA2 and CA3;
- strata with the less dense cell bodies, such as stratum moleculare of the cornu Ammonis and the dentate gyrus of both sides of the hippocampal sulcus, and the adjacent stratum moleculare of the subiculum

• the alveus covering Ammon's Horn

The part of the dentate gyrus is less well defined. It is clearly not possible to distinguish only the stratum granulosum of the dentate gyrus with this resolution. In addition, there is an ambiguity, as it appears in opposite contrast in certain post-mortem sequences. It is not possible to segment all structures by focusing only on the intensities. Thus, geometric and spatial coherence are incorporated to facilitate the implementation of the segmentation.

In the head, the segmentation is much more complex, given the presence of hippocampal digitations. The consistency of the 3D sagittal and axial sections is also essential to understand the nested arrangement of the structures.



Figure 7.9: Steps of the manual delineation of the subparts of the hippocampal formation, in a coronal slice of the body. Purple: alveus; green: CA-WM; light blue: DG; dark blue: CA-GM; white: subiculum-GM; yellow: subiculum-WM.

Based on our ability to consistently identify substructures in the hippocampal formation, we selected six labels for the segmentation, which are delineated in this precise order:

- the *alveus*;
- a label combining the stratum radiatum and stratum lacunosum-moleculare of the CA1-CA3 fields (the dark band around the dentate gyrus), referred to as *CA-WM*;
- the dentate gyrus and the CA4 field, referred to as *DG*;
- the stratum pyramidale of the cornu Ammonis, referred as CA-GM;
- the stratum pyramidale of the subiculum, referred as *subiculum-GM*;
- the stratum moleculare of the subiculum, referred as *subiculum-WM*

7.4 Application to create a 3D atlas

We applied the manual delineation protocol described in the previous sections to a postmortem specimen in order to create a 3D atlas of hippocampal subregions with very high and quasi-isotropic resolution.

The postmortem specimen is one of the samples from [Yushkevich et al., 2009] (referred as subject 1R). The image acquisition procedure is described in [Yushkevich et al., 2009] and a few elements are given below. This image was acquired on a 9.4 Tesla Varian 31 cm horizontal bore scanner (Varian Inc, Palo Alto, CA). The sample was placed in leak-proof bags and wrapped with plastic to fit snugly inside the coil. Scanning parameters were: matrix size: 350x256; field of view: 70x77 mm. Acquisition time was 13h13. The acquisition used the standard multi-slice spin echo sequence with TR=4s, and TE=26 ms. An oblique slice plane was chosen to cover the hippocampus with as few slices as possible, requiring 120 slices with 0.2mm slice thickness. The sample was scanned at 0.2x0.3x0.2 mm resolution using 34 averages to achieve good contrast (the scan was acquired overnight).

This resulted in a 3D digital model of the different suregions, which is topologically correct and preserves the circonvolutions of the structure. Some example slices are shown in figure 7.10. Some 3D renderings are shown on figure 7.11. After the publication of the corresponding paper, we plan to make this atlas available online.



Figure 7.10: 3D atlas of hippocampal subregions. Coronal views of the hippocampus and subregions labels. The slices shown are the same than in figure 7.3, in the tail, body and head. See figure 7.9 for the colour legend. One can note that the convolution of Ammon's horn are well-preserved.

7. BUILDING AN ATLAS OF HIPPOCAMPAL INTERNAL STRUCTURE FROM POST-MORTEM MRI



Figure 7.11: 3D views of the atlas of hippocampal subregions. The different subregions (DG in light blue, CA-WM in green, CA-GM in dark blue, subiculum-GM in white, subiculum-WM in yellow, alveus in purple) are progressively superimposed from left to right and top to bottom.



REPRODUCING KERNEL HILBERT SPACES

This chapter provides a brief introduction to Reproducing Kernel Hilbert Spaces (RKHS) which are central to the methods proposed in the next chapters.

8.1 Elements of Hilbert Space Theory

8.1.1 Definitions

A vector space H over \mathbb{R} is a Hilbert space if

- *H* has a norm induced by an inner product denoted (*h*, *h*') → ⟨*h*, *h*'⟩_H. The associated norm is ||*h*||²_H = ⟨*h*, *h*⟩_H
- *H* is a complete space for the topology associated to the norm

If the first condition is weakened to the fact that the norm $\|.\|$ is not induced by an inner product, one says that *H* is a Banach space. If *H* satisfies only the first condition, it is called a pre-Hilbert space.

Theorem 8.1.1 (Schwartz inequality) On a pre-Hilbert space H, Schwartz inequality holds: $\forall h, h' \in H$,

$$\langle h, h' \rangle_H \leq \|h\|_H \|h'\|_H$$

A Hilbert space isometry between two Hilbert spaces *H* and *h'* is an invertible linear map $F: H \to H'$ such that, for all $h, h' \in H$, $\langle Fh, Fh' \rangle_{H'} = \langle h, h' \rangle_{H}$

The dual space of a normed vector space *H* is the space containing all continuous linear functionals $\Phi : H \to \mathbb{R}$. It is denoted H^* . We will use the notation $\Phi(h) = (\Phi, h)$ for $\Phi \in H^*$ and $h \in H$.

H being a normed space, H^* also has a normed space structure, defined by

$$\|\Phi\|_{H^*} = max\{(\Phi, h) : h \in H, \|h\|_H = 1\}$$

Let *H* be a Hilbert space. For all $h \in H$, the function $\Phi_h : h' \to \langle h, h' \rangle_H$ belongs to *H'*, and by Schwartz inequality we have $\|\Phi_H\|_{H^*} = \|\Phi\|_H$.

Theorem 8.1.2 (Riesz representation theorem) *Let* H *be a Hilbert space. If* $\Phi \in H^*$ *, there exists a unique* $h \in H$ *such that* $\Phi = \Phi_h$.

Thus, the Riesz representation theorem identifies a Hilbert space *H* to its dual H^* . With a slight abuse of notation, we will identify *h* and Φ_h .

8.1.2 Reproducing Kernel Hilbert Space

Let $\Omega \subset \mathbb{R}^d$ and *V* a Hilbert space embedded in $C^0(\Omega, \mathbb{R}^d)$. Let $x \in \Omega$, the linear function δ_x defined by $(\delta_x, v) = v(x)$ is called the evaluation function. If δ_x is continuous on *V*, *V* is called a Reproducing Kernel Hilbert Space(RKHS). For all $\alpha \in \mathbb{R}^d$, we will denote $a \otimes \delta_x$ the linear form such that $(a \otimes \delta_x || v) = \alpha^T v(x)$. By Riesz theorem, there exists an element $K_x^\alpha \in V$ such that, for any $v \in V$,

$$\langle K_x \alpha, \nu \rangle_V = \alpha^T \nu(x)$$

The map $\alpha \Rightarrow K_x^{\alpha}$ is linear from \mathbb{R}^d to *V*, which implies that, for $y \in \Omega$, the map $\alpha \Rightarrow K_x^{\alpha}(y)$ is linear from \mathbb{R}^d to \mathbb{R}^d . We will note K(y, x) the matrix such that, for $\alpha \in \mathbb{R}^d$, $x, y \in \Omega$, $K_x \alpha(y) = K(y, x)\alpha$.

This function *K* is called the reproducing kernel of *V*, and has several interesting properties, such as the self-reproducing property:

$$\forall x, y \in \Omega, \alpha, \beta \in \mathbb{R}^d, \langle K(., x)\alpha, K(., y)\beta \rangle_V = \alpha K_V \beta(x) = \alpha_T K(x, y)\beta$$

By symmetry of the inner product, we obtain : $K(y, x) = K(x, y)^T$.

A second property is that *K* is positive definite, in the sense that, for any family $x_1, \ldots, x_n \in V$ and any $\alpha_1, \ldots, \alpha_n$:

$$\sum_{i,j=1}^{n} \alpha_i \alpha_j K(x_i, x_j) \ge 0 \sum_{i,j=1}^{n} \alpha_i \alpha_j K(x_i, x_j) = 0 \Leftrightarrow \alpha_1 = \dots = \alpha_n = 0$$
(8.1)

For any $v \in \mathcal{V}^*$, we have $||v||_{V^*}^2 = \int_{\Omega} v(x)^T K(x, y) v(y) dx dy$.



SHAPE MODELING OF THE HIPPOCAMPAL RIBBON AND THICKNESS ESTIMATION

In this chapter, we introduce a framework for the computational anatomy of one of the main subregions of the hippocampus, which we call the hippocampal ribbon. This ribbon corresponds to the gray matter of Amon's horn and of the subiculum (denoted as CA-GM and subiculum-GM in the previous chapter). We chose to consider these two structures altogether since they are contiguous and since the limit between the subiculum and Ammon's horn is defined only geometrically and is not visible on the images.

The hippocampal ribbon is a laminar structure, and could be compared to a highly convoluted sheet. The hippocampus is horizontally organized as a superposition of layers (see section 2.4). This two-dimensional organization within the sheet suggests that, like for the cortex, its thickness is a fundamental measurement to study its anatomy. We thus chose to model this structure as a skeleton and a thickness measure.

Here, we propose a method to compute a skeleton for thin surfaces as well as a robust estimation of the thickness based on an original variational formulation. The proposed functional is carefully designed to include a proper regularization term which prevents the analysis from numerical instability usually present in standard skeletonization approaches. We first introduce the desirable properties of an appropriate thickness measurement and show how our variational formulation leads to a well-posed problem as well as an effective maximization procedure. We conclude this chapter with the evaluation of the method on synthetic shapes.

9.1 Requirements for thickness measures

There is no widely accepted definition of thickness, and different metrics were introduced to compute an estimation of cortical thickness (see section 3.2.4). An appropriate measurement of the hippocampal thickness should verify some desirable properties.

9. SHAPE MODELING OF THE HIPPOCAMPAL RIBBON AND THICKNESS ESTIMATION



Figure 9.1: Exemple of problem which can occur when using a definition of thickness based on straight lines (here, the closest-point method). We can see that this definition is not symmetric: we do not get the same measure if we interchange inner and outer surfaces. Moreover, the point x' is associated with two points on the outer surface.

First, we would like the definition of thickness to be consistent with the horizontal lamination of the hippocampus. For example, some definitions of the thickness are based on the computation of the radius of maximal enclosing balls [Fletcher et al., 2004; Yushkevich et al., 2003]. The two spokes emanating from a point on the medial surface form a broken line whose length doesn't give an anatomically plausible thickness measure.

In the same way, the path used to compute the thickness can't be a straight line, because it's not realistic in regions with high curvature and can lead to a non-symmetric definition of thickness (figure 9.1), as well as to ambiguities. In this context, the thickness has to be a volumetric measurement: thickness would be computed in the entire volume, and each point in the volume has to be associated with a unique value. In practice, this means that pathlines of thickness between boundaries may not intersect.

Moreover, to be an efficient analysis tool, the computation of thickness has to satisfy both accuracy and robustness requirements. Accuracy of the measurement reflects its ability to correctly define the distance between the boundaries of the structure considered, as defined by manual measurements or simulations with known thickness. A measurement can be declared robust if it provides reproducible results from repeated estimations. Therefore, definition of thickness has to overcome small pertubations on the boundaries, due to discretization, and be invariant under acquisition parameters such as orientation.

9.2 Shape modeling of the hippocampal ribbon and thickness estimation

In this section, we propose a variational approach to simultaneously extract the *skeleton* and local thickness measurements of the hippocampal ribbon. This is done by estimating a

smooth vector field which goes through the ribbon. This approach relies on representations of such vector fields using the theory of reproducing kernel Hilbert spaces. Thickness is then computed as the length of the streamlines from one boundary to the other, following the vector field. Note that the following methodology can be applied either to the full volumic segmentation (3D case) or separately to each coronal slice (2D case).

9.2.1 Vector field estimation using a variational approach

Our method computes thickness from flow lines defined between the two boundaries. This is similar to the Laplace method firstly described in [Jones et al., 2000], but unlike Jones, we prefer to directly estimate trajectories from a transverse vector field rather than to define it as the gradient of a function.

We will construct a smooth vector field v which runs from the inner boundary to the outer, in order to establish correspondance trajectories between these two frontiers. Thickness can be defined as the length of these trajectories. To meet the requirements defined in the previous section, the vector field must satisfy some desirable properties:

- 1. Uniqueness : Lines can't cross
- 2. The field must go through the volume by following the thinner direction, i.e to go as directly as possible from the inner to the outer boundary.
- 3. The field must be smooth enough.
- 4. No trajectories must stop inside the volume.

To that purpose, we define the transverse vector field as the solution of an original variational formulation.

Let $\Omega \subset \mathbb{R}^d$, be the hippocampal ribbon, with d = 2 or d = 3, $\partial \Omega$ its boundary and *n* the outward normal to $\partial \Omega$.

We decompose the boundary $\partial \Omega$ into its inner, outer and "wall" parts: $\partial \Omega = \partial \Omega_i \cup \partial \Omega_o \cup \partial \Omega_w$.

Considering the vector field as the deplacement of a set of particles, one can see the inner frontier as the entrance, while the outer frontier is the exit and the "wall" part puts up a barrier avoiding the leak of the particles.

Let $\epsilon : \partial \Omega \rightarrow \{-1; 0, 1\}$ be the function defined by :

 $\epsilon = -1 \quad \text{in} \quad \partial \Omega_i \tag{9.1}$

$$\epsilon = 0 \quad \text{in} \quad \partial \Omega_w \tag{9.2}$$

$$\epsilon = 1 \quad \text{in} \quad \partial \Omega_o.$$
 (9.3)

This function defines the orientation of the normal vector in $\partial \Omega$ ($\epsilon = 1$ for a outward orientation and $\epsilon = -1$ for an inward orientation).

We then estimate the vector field v maximizing the following functional:

$$J(u,v) = \int_{\partial\Omega} \langle v, \epsilon n \rangle \, d\sigma + \int_{\Omega} \langle v, u \rangle \, dx - \frac{1}{2} \, \|v\|_{V}^{2} \tag{9.4}$$

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Figure 9.2: Initial estimation of ϵ in the head of the hippocampus. The manual segmentation of hippocampal supparts is shown on panel **A**. The hippocampal ribbon (stratum pyramidale of the Cornu Ammonis and subiculum) is in dark blue, the gyrus dentatus is in light blue, alveus is in green and the strata with the less dense cell bodies are in yellow. The points adjacent to the alveus or CA/subiculum-WM are assigned to the outer or inner boundary respectively (red points on panels **B** and **C**. The value of ϵ for the remaining points of the boundary (red points on panel **D**) will be evaluated during the optimisation of the functional *J*.

where *u* is a unit vector field on Ω and $\|.\|_V$ is the Hilbert norm of $v \in V$, a Reproducing Kernel Hilbert Space (RKHS).

The first term is the "unsigned" flux of the vector field. It drives the field in a direction close to the normal to the surface. The second term enforces vectors in Ω to not have zero norm, in order to construct continuous streamlines inside the volume. The last term controls the regularity of the vector field. By controlling its norm, we ensure that it will be smooth enough and not suffer from small irregularities in the boundaries. Note that the use of a regularizing kernel provides diffeomorphics flows and avoids possible crossing of streamlines.

The outer and the inner boundaries, or, equivalently, the value of ϵ , do not need to be marked everywhere by the user. If the user only marks part of the boundaries, the remaining values of ϵ will be estimated by optimizing on $J(u, v, \epsilon)$.

In practice, we automatically assign to the inner boundary the points adjacent to the strata with the less dense cell bodies of the Cornu Ammonis and the subiculum (called CA-WM and subiculum-WM in the chapter 7) and represented in yellow in the figure 9.2, while the points adjacent to the alveus (in green) are marked as the outer boundary. It remains some points which can't be directly assigned to the outer or inner boundary (panel B of figure 9.2): the value of ϵ at these points while be estimated during the procedure.

9.2.2 Maximization of the functional

From the theory of RKHS of vector fields, we know that space *V* is characterized by the choice of a kernel $K : \mathbb{R}^d \times \mathbb{R}^d \to \mathbb{R}$, such that, for any $(v, x, \alpha) \in V \times \mathbb{R}^d \times \mathbb{R}^d$,

$$\langle v(x), \alpha \rangle_{\mathbb{R}^d} = \langle v, K(., x) \alpha \rangle_V \tag{9.5}$$

Optimization in *u*, for *v* fixed, is straightforward : $u = \frac{v}{\|v\|}$. Optimization on ϵ is done only on the unknown regions (where ϵ was not automatically marked) : $\epsilon = \text{sgn}(\langle v, n \rangle)$. Elsewhere, values of ϵ are fixed.

Now, if u and ϵ are fixed, the problem is quadratic and v can be easily calculated from the formula:

$$\nu(x) = \int_{\partial\Omega} K(x, y) \epsilon(y) n(y) d\sigma(y) + \int_{\Omega} K(x, y) u(y) dy$$
(9.6)

Proof : We have for any variation δv

$$\frac{\partial J}{\partial \nu} \delta \nu = \int_{\partial \Omega} \langle \delta \nu, \epsilon n \rangle + \int_{\Omega} \langle \delta \nu, u \rangle - \langle \nu, \delta \nu \rangle_{V} = 0$$
(9.7)

Choosing $\delta v = K(., x)\alpha$ and using property 9.5 in the last term of 9.7 implies that:

$$\langle v(x), \alpha \rangle = \int_{\partial \Omega} \langle K(., x)\alpha, \epsilon n \rangle + \int_{\Omega} \langle K(., x)\alpha, u \rangle$$
(9.8)

	Using the relation	9.6 in the	functional	implies that:
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$$J(u,v) = \frac{1}{2} \int_{\Omega} u(y)^{T} K(x,y) u(x) dx dy + \int_{\partial \Omega} \epsilon(y)^{T} n(y) K(x,y) \epsilon(x) n(x) d\sigma(x) d\sigma(y)$$

$$= \frac{1}{2} \| u + \epsilon n \|_{V}^{*}$$

Thus, the variational formulation leads to a problem involving the maximization of a dual norm on vector fields. Smoothness of v is related to the fact that the linear form $u + \epsilon n$ has a large dual norm. It could seem surprising to use a dual norm as a measure of smoothness. For a vector field, a small dual norm is not an indication of smoothness but the opposite : if the vector field is very noisy, the averaging effect of the kernel will result in a small dual norm. On the opposite, if the vector field v is smooth, the vector fields v(x) and K(x, y)v(y) will be very similar, and $||v||_{V^*}$ will take large values.

9.2.3 Streamlines computation and estimation of thickness

Given the vector field $v : \Omega \to \mathbb{R}^d$, one can compute the *trajectory traced by a point* $x_0 \in \Omega$ following v. This path is called a streamline. Streamlines exhibit some properties :

- Since the flow is diffeomorphic, the streamlines can never cross.
- Any point on Ω has a unique streamline going through it, connecting a point on the boundary to the opposite boundary. The length of a streamline starting from a point $x \in \Omega$ defines the thickness at this point
- The value of the thickness along a streamline is constant.

For each point $x \in \Omega$, we define thickness as the summation of the length of two different streamlines, one that follows the field v towards the outer boundary, and another that follows the field -v and reaches the inner boundary.

We note $P_+(x)$ and $P_-(x)$ the two streamlines, starting from x and following the fields v and -v respectively. Thickness at point x is defined as the sum of $D_+(x) = \text{length}(P_+(x))$ and $D_-(x) = \text{length}(P_-(x))$, while the skeleton is defined as the zero level set of the function $D_+ - D_-$.

9.2.4 Extension to anisotropic images

High field images offer in-plane submillimetric resolution that allows visualizing the inner structure of the hippocampal structure but are highly anisotropic. Inter-slice interpolation is a hard problem, due to to the convoluted shape of digitations in the hippocampal head. Instead, we introduce an anisotropy term in the functional to implicitly take into account the slice thickness while still working with raw data (without interpolation). We detail below how to extend the variational formulation.

Let Φ be an application that maps a volume Ω in "physical"space (the "brain"space) to a volume $\tilde{\Omega} = \Phi(\Omega)$ in the image space. In our case, Φ is a linear transformation of type $\Phi(x, y, z) = (x, y, z/a)$ where *a* is the anisotropy factor. We define $\Psi = \Phi^{-1}$, *A* the matrix of the application $D\Phi$, \tilde{n} the normal at $\partial \tilde{\Omega}$.

Let K_p be the kernel in physical space and K_i the kernel in image space, such as $K_i(x, y) = K_p(\Phi(x), \Phi(y))$, and V_p , respectively V_i , the RKHS of K_p and K_i .

Thus \tilde{v} , the vector field in the image space, is given by:

$$\tilde{\nu}(x) = \int_{\tilde{\Omega}} K_i(x, y) \frac{u(y)}{\det(A)} dy + \int_{\partial \tilde{\Omega}} K_i(x, y) \tilde{\epsilon}(y) \frac{A^T \tilde{n}(y)}{\det(A)} d\tilde{\sigma}(y)$$
(9.9)

Proof $\forall v \in V_p$, we have $v \circ \Psi \in V_i$ and $||v||_{V_p} = ||v \circ \Psi||_{V_i}$. By substitution in the standard variational formulation we get :

$$J(u,v) = \int_{\partial\Omega} \langle v, \epsilon n \rangle \, d\sigma + \int_{\Omega} \langle v, u \rangle \, dx - \frac{1}{2} \, \|v\|_{V}^{2}$$
(9.10)

$$= \int_{\partial \tilde{\Omega}} \langle v \circ \psi, \epsilon n \circ \psi \rangle \det(D\Psi) d\tilde{\sigma}$$
(9.11)

$$+\int_{\tilde{\Omega}} \langle v \circ \Psi, u \circ \Psi \rangle \det(D\Psi) dx - \frac{1}{2} \| v \circ \Psi \|_{V_i}^2$$
(9.12)

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Considering that $\partial\Omega$ is defined implicitly as the zero level set of a function *F*, then at a point $x \in \partial\Omega$, the normal n(x) is given by $n(x) = \nabla F(x)$. The surface $\partial\tilde{\Omega}$ and the normal $\tilde{n}(\tilde{x})$ at any point $\tilde{x} = \Phi(x) \in \partial\tilde{\Omega}$ are respectively given by $F \circ \Psi$ and $\nabla (F \circ \Psi)(\tilde{x}) = D\Psi(y)^T n(x)$ If we set $\tilde{v} = v \circ \Psi$ and $\tilde{u} = u \circ \Psi$, the first and second terms of 9.11 become:

$$\int_{\partial \tilde{\Omega}} \frac{\langle \tilde{v}, A^T \epsilon \tilde{n} \rangle}{\det(A)} d\tilde{\sigma} \text{ and } \int_{\tilde{\Omega}} \frac{\langle \tilde{v}, \tilde{u} \rangle}{\det(A)} dx$$

Applying the same reasoning as in the isotropic case leads to the result.

9.2.5 Implementation details

9.2.5.1 Discretization

We assume that the volume Ω is discretized over a grid: we denote by *I* the set of the voxels of the volume, and *B* the boundary voxels. Integrals are approximated by sums. Let x_i, x_j represent points on the grid. Denoting $K_{i,j} = K(x_i, x_j)$ and $u_i = u(x_i)$. The discretized formulation of the square of the dual norm is given by

$$\frac{1}{2} \left(\sum_{x_i, x_j \in I} K_{i,j} \langle u_i, u_j \rangle + \sum_{x_i, x_j \in B} K_{i,j} \langle \epsilon_i n_i, \epsilon_j n_j \rangle + 2 \sum_{x_i \in I, x_j \in B} K_{i,j} \langle u_i, \epsilon_j n_j \rangle \right)$$
(9.13)

9.2.5.2 Kernel

The choice of an appropriate kernel is a crucial point. Indeed, the similarities between pair of points (here, vector fields) are expressed in terms of the kernel function: $K : \Omega \times \Omega \rightarrow \mathbb{R}$. Thus, the kernel defines the structure of the RKHS.

The function *K* must satisfy two mathematical requirements:

- It must be symmetric: $\forall (x_1, x_2) \in \Omega$, $K(x_1, x_2) = K(x_2, x_1)$
- It must be positive semi-definite

In the discrete case, the kernel *K* can be represented by a matrix, the Gram Matrix, which we shall denote by the same letter *K* without risk of confusion 1 .

However, the computation of the Gram Matrix can be time-consuming, instead we will use a recursive implementation of the kernel. The recursive method proposed below has several advantages:

• The kernel fits the geometry of the considered structures, even the convoluted ones.

¹Indeed, the matrix and the function inherit the properties of symmetry and positive semidefiniteness.

• It can be easily extended to anisotropic cases.

In this section, we will consider kernels based on random walks on undirected graphs. Let's begin with some definitions.

We denote a weighted graph by the triple $\Gamma = (G, E, w)$ where *G* is the set of nodes, $E \subset G \times G$ is the set of edges and $w : G \times G \to \mathbb{R}$ is a weight function. We will consider first an unweighted graph: $w(x, y) = 1 \forall (x, y) \in E$; w(x, y) = 0 otherwise.

Isotropic case Let *A* be the adjacency matrix defined by $A(x, y) = \begin{cases} 1 & \text{if } (x, y) \in E \\ 0 & \text{otherwise} \end{cases}$ Further, let $D = diag(d(x); x \in G)$ be the diagonal degree matrix with elements $d(u) = \sum_{y=1}^{|G|} A(x, y)$: d(x) is the number of neighbors of the node *x*.

A loop is an edge that connects a vertex to itself. If a graph contains a loop at a node x, then A(x, x) = 1

A random walk on a graph is a process that begins at some node, and at each time step moves to another node with a fixed probability.

If a graph contains loops at each node, then the walk is called "lazy", since the walk has the choice to stay in its current position at each step.

Consider a graph with loops at each node, and the random process that starts from some node $x \in G$, and repeatedly moves to a neighbor node y chosen with probability h(x, y) or stays in its current position with the probability h(x, x). This type of process is a lazy random walk.

The function *h* is defined as : $h(x, y) = \begin{cases} d(x)^{-1} & \text{if } (x, y) \in E \\ 0 & \text{otherwise} \end{cases}$ Let *S_t* denote the position of the walk at a time *t*. If the walk starts at some node $x_0 \in G$,

Let S_t denote the position of the walk at a time t. If the walk starts at some node $x_0 \in G_t$ then $S_0 = x_0$. We will let the vector $p_t \in \mathbb{R}^{\|G\|}$ denote the probability distribution at time t.

We will write $p_t(x)$ to indicate the value of p_t at a node x: $p_t(x)$ is the probability of being at node x at time t.

$$p_t(x) = \mathcal{P}(S_t = x) \tag{9.14}$$

Thus, the initial probability distribution, p_0 , will typically be concentrated at one node: the walk starts at some node x_0 , which implies $p_0(x_0) = 1$ and $p_0(x) = 0$, $\forall x \neq x_0$.

To derive p_{t+1} from p_t , note that the probability of being at a node x at time t + 1 is the sum over the neighbors y of x (including itself) of the probability that the walk was at y at time t, times the probability it moved from y to x in time t + 1.

Algebraically, we have:

$$p_{t+1}(x) = \sum_{y \in G} \frac{1}{d(y)} p_t(y) = \sum_{y \in G} h(x, y) p_t(y).$$
(9.15)

This can be written in matrix form:

$$p_{t+1} = D^{-1}Ap_t \tag{9.16}$$

We introduce the probability matrix of the lazy random walk on the graph *G*: $H = D^{-1}A$. We have:

$$p_{t+1} - p_t = (H - I)p_t = D^{-1}(A - D)p_t$$
(9.17)

Note that the matrix H - I is known as the normalized Laplacian Matrix. Thus, the equation 9.17 is a diffusion equation. To illustrate this diffusion process, imagine some substance such as gas or fluid is deposited on each node. At each time step, some of the substance diffuses out of each node vertex: a part stays at the node, the rest is distributed among its neighboring vertices, then the distribution of the substance will evolve according to equation 9.17.

By iterating the relation in 9.16, we have the following relation:

$$p_t = H^t p_0 \tag{9.18}$$

However, the matrix H^t is not symmetrical, and can't be used as a Gram Matrix. We introduce a slight modification to the matrix H^t to symmetrize it, and define the kernel $K_t = \tilde{H}^t = (D^{\frac{1}{2}}HD^{-\frac{1}{2}})^t = (D^{-\frac{1}{2}}AD^{-\frac{1}{2}})^t$. Thus, the diffusion weights $\tilde{h}(x, y)$ are defined as:

$$\tilde{h}(x,y) = \frac{1}{\sqrt{d(x)d(y)}}$$
(9.19)

The two properties of a kernel are respected: K_t is symmetric since A is symmetric; and K_t is definite positive. The size of the kernel will increase with the value of t.

We now explain the formulation of the kernel in the simplest case. We stand here in a 2D case, but the extension to 3D is direct. Consider first that all points of the image are nodes, and that they are all connected with their 4-connexity neighborhood and with theirselves.²

Thus we consider the image as a whole, without taking into account the morphology of the object, and the weight $\tilde{h}(x, y)$ associated to each point is $\frac{1}{5}$. This can be seen on figure 9.3. As soon as one considers regions with high curvature, some difficulties arise. Indeed, if the hippocampal ribbon is highly folded, bands of grey matter with opposite orientation are close, and the inner (or outer) surface of the layer has two nearby sides. The size of the kernel has to be smaller than the distance separating the two sides of the surface. If this condition is not respected, the regularization step averages vectors with oppposite directions, and the estimation of the transverse direction is biased. To overcome this difficulty, a simple-minded idea consists of using kernels with little values of *t*. However, we would be constrained to choose *t* of the order of the pixel size, since in the extreme case the two bands are in contact (due to partial volume effect). As a result, the vector field would be poorly regularized, and the transverse direction would be misestimated.

We propose to adapt the kernel to take into account this type of configuration. In general, the idea is to locally adapt the kernel to the geometry of the volume. To this purpose, we will consider that a point $y \in G$ is in the neighborhood of a point $x \in G$ if it is in Ω and if it is in the 4-neighborhood of x, or if x = y. Thus, the diffusion is restricted to Ω , and the kernel is adapted to its shape. Figure 9.4 shows an example of the diffusion coefficients in this case. In the following, we will use this type of kernels for our experiments.

Anisotropic case The in-vivo MRI acquisitions of hippocampal subregions are anisotropic. Indeed, the images used in chapter 12 have a resolution of 250 $\mu m^*250 \mu m^*1 mm$, ie a factor of anisotropy of 4 in *z*. We take into account this anisotropy by introducing a weighted graph:

²We neglect here the potential border effects, considering that the object of interest is away from the edges of the image

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Figure 9.3: In the simplest case, we compute the diffusion coefficients $\tilde{h}(x, y)$ without considering the morphology of the object. At each time step *t*, the diffusion at point *x* is distributed homogeneously among their 5 neighbours.

when the graph is weighted, the probability that the vertex moves to a neighbor depends on the weight of the corresponding edge. In our case, the weights will depend on the factor of anisotropy of the image. Consider a 2D case, and suppose we have a factor of anisotropy of *l* in the vertical axis (ie the resolution image is X*IX mm.) We assign the weights $\alpha = \frac{5l^2}{3l^2+2}$ to the horizontal edges and loops, and $\beta = \frac{5}{3l^2+2}$ to the vertical edges (see figure 9.5), and modify the adjacency matrix as follows:

$$\tilde{A}(x, y) = \begin{cases} w(x, y) & \text{if } (x, y) \in E \\ 0 & \text{otherwise} \end{cases}$$
(9.20)

Thus, we will obtain a value of $\sqrt{\frac{\alpha}{\beta}} = l$ for the ratio between the extent of the kernel in the horizontal axis relative to the vertical axis. An example of anisotropic kernels is shown on figure 9.6.

9.3 Experiments on synthetic datasets

9.3.1 Hairpin

We consider a folded ribbon, determined by two parameters: its thickness *T* and the distance d = 2 * 15 - T between the two sides of the ribbon as depicted on figure 9.7.

In the following experiment, we fix the thickness T to 14 and the distance d to 2, and study the influence of the parameter t of the kernel (which determines its size) and compare



Figure 9.4: Computation of diffusion coefficients for the kernel restricted to Ω . The point x has three neighbours: itself, the point x_a situated below it, and the point x_r at its right. The diffusion coefficient $\tilde{h}(x, x)$ is equal to $\frac{1}{3}$. The point x_a is situated within the volume Ω and has five neighbours, while the point x_r , situated at the frontier, has three neighbours. Thus, the diffusion coefficients $\tilde{h}(x, x_a)$ and $\tilde{h}(x, x_r)$ are respectively equal to $\frac{1}{\sqrt{5*3}} = \frac{1}{\sqrt{15}}$ and $\frac{1}{\sqrt{3*3}} = \frac{1}{3}$.

the behaviors of different types of kernel (defined on the entire image or adapted to the geometry of the ribbon). We demonstrate here how the choice of an appropriate kernel is crucial: we compute the weights of the kernel at a pixel x in the inner boundary of ribbon for the two types of kernels described above (the size parameter t is set at 7). In figure 9.8, we can see in the first case that positive values are assigned to pixels located on the oppposite side, and on the space between the two sides. This will lead to average vectors with different orientations, and the resulting vector will deviate from the normal direction. In contrast, in the second case, the shape of the kernel follows the boundaries of the ribbon. Figure 9.9 shows the behavior of the algorithm depending one whether one uses the first or the second kernel with growing sizes, in case of close branches (d=2). One can see that results are more accurate when using the adaptated kernel, and less sensitive to the choice of the size of the kernel.

9.3.2 Sinusoid

Here, we used a synthetic phantom with a sinusoid shape (Figure 9.10). Let f be the function given by :

$$f(x, y) = x - \alpha * \sin(2\pi y, x) \in \mathbb{R}, y \in [-1, 1]$$
(9.21)

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Figure 9.5: Anisotropic kernels are built by introducing different weights for loops and horizontal or vertical links.



Figure 9.6: Left: Isotropic diffusion kernel (l=1,t=15). Right: Anisotropic diffusion kernel (l=2,t=15).

The inner and outer boundaries are the *r* and *R* level sets of the function *f*, respectively (with r < R). The theoretical skeleton is the (r + R)/2 level set of *f*.

We tested our algorithm with different kernel sizes and compared the true and the estimated location of the skeleton. We set r = 5, R = 15 and $\alpha = 15$. We can observe in figure 9.11 that the skeleton points are close to their expected position.

9.3.3 Sphere

We tested our algorithm in 3D on a set of phantom images at different image resolutions and anisotropy. In the simplest case, the outer boundary is a sphere of radius *R* and the inner boundary is a sphere of radius *r*, with r < R. The ribbon is a spherical shell of thickness R - r. Thus, we can compare the result of our algorithm with a ground truth. We created phantoms with values of r = 19 and R = 25 with resolutions 1 * 1 * 1, 0.5 * 0.5 * 0.5, 1 * 1 * 0.5 and 0.5 * 0.5 * 1. The expected thickness is 6 mm.

Table 9.1 displays the estimated thickness values for the different resolutions. One can



Figure 9.7: Folded ribbon. T: thickness of the ribbon; d: distance between the two branches.



Figure 9.8: When the kernel is defined on the entire image (on the left), regularization overflows outside the shape and up to opposite branches. If the kernel is defined from the graph of the shape (on the right), regularization respects its geometry.

see that, overall, thickness is correctly estimated. However, as expected, the accuracy of the estimation slightly decreases when resolution decreases and anisotropy increases.

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Figure 9.9: Mean thickness error for the hairpin with distance d = 2 between the two branches. Circles are for the kernel adapted to the geometry of the shape, triangles are for the kernel in the entire image.



Figure 9.10: Sinusoid shape

9.3.4 Ribbon

In this case, we consider a shape with undulations mimicking gyri. Similar shapes have been used in [Das et al., 2009]. The outer boundary is defined as the set of points such as

$$R + \gamma \sin(\alpha \Phi) = T \tag{9.22}$$

where (Θ, Φ, T) is expressed in spherical coordinates.

The inner boundary is defined as the set of points verifying

$$r + \gamma \sin(\alpha \Phi) = T \tag{9.23}$$

The parameters *r* and *R* determine the radius of the boundaries, while γ and α control the magnitude and the frequency of the undulations of the surface. In the following, we set the parameters to *R* = 20, *r* = 14, γ = 4 and α = 5. An example of such a phantom is shown on



Figure 9.11: Sinusoid shape: position of the computed skeleton. The graph displays the mean value of the function f on the skeleton points, depending on the size parameter t. The theoretical skeleton points verify f = 10.

Table 9.1: Comparison of thickness for the synthetic spherical shell with different resolu-tions. Expected thickness is 6.

Resolution	Mean	Std	Min	Max
1*1*1	6.02	0.25	5.09	6.68
0.5*0.5*0.5	6.01	0.13	5.55	6.37
1*1*0.5	6.18	0.35	4.73	7.53
0.5*0.5*1	6.18	0.21	5.45	6.97
2*2*2	5.94	0.42	4.62	6.67

Figure 9.12. We do not have a ground truth for the thickness, but we expect that the skeleton points will verify the following relation:

$$\frac{r+R}{2} + \gamma \sin(\alpha \Phi) = T \tag{9.24}$$

In the following, we compare results obtained on phantoms with resolutions 1 * 1 * 1, 0.5 * 0.5 * 0.5, 1 * 1 * 0.5, 0.5 * 0.5 * 1 and 2 * 2 * 2

In table 9.2, we can see that the results are relatively reproducible through the changes in resolution or the anisotropy in the slice thickness.

In figure 9.13, the expected skeleton is superimposed with the skeleton obtained with the algorithm on the phantom with resolution 0.5 * 0.5 * 0.5. We can see that the two skeletons are very close.

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Figure 9.12: Section and volumetric representation of the ribbon-shaped phantom.

Table 9.2: Comparison of the thickness for the synthetic 3D phantom with different resolutions.

Resolution	Mean	Std	Min	Max
1*1*1	4.95	0.80	3.22	6.80
0.5*0.5*0.5	4.90	0.73	3.55	6.35
1*1*0.5	5.22	0.88	2.97	7.63
0.5*0.5*1	5.07	0.79	3.09	6.94
2*2*2	5.13	0.94	2.82	7.24

9.4 Conclusion

In this chapter, we have proposed a method to model the hippocampal ribbon as a skeleton and a thickness measure. This approach is based on an original variational formulation which includes a proper regularization using RKHS. This provides a diffeomorphic flow between the inner and outer surfaces. We proposed an original kernel implementation which can handle both isotropic and anisotropic cases. The evaluation of the methods on synthetic shapes demonstrates that it provides accurate thickness measures and skeleton positioning. In the following chapters, we will validate the approach using the postmortem atlas proposed in chapter 7 and apply it to in vivo data acquired at 7T.



 $Figure \ 9.13: \ Superimposition \ of the \ estimated \ skeleton \ with \ the \ "ground \ truth"$


VALIDATION USING THE POSTMORTEM ATLAS

There is no ground truth of thickness measures, since its manual marking is not feasible. In this chapter, we propose to validate the reliability of our method by using the postmortem atlas that we previously built (chapter 7). Based on this atlas, we implemented an experiment, designed to test for reliable thickness estimation within one patient. We virtually create different scans of the same subject, by changing the value of the slice thickness of the acquisition.

10.1 Materials and methods

We first run the algorithm on the original segmentation of the atlas. The atlas has a very high resolution, with quasi-isotropic voxel size, this thus enables us to estimate with high precision the thickness of the hippocampal ribbon in 3D.

The thickness estimation method can be applied to both 2D and 3D data. Here, we compared the results obtained in 3D to those obtained in 2D.

Finally, since the in vivo 7T MR images (that will be analyzed in the next chapters) are not isotropic, we wanted to test whether the method is robust to changes in slice thickness. To that purpose, we subsampled the original segmentation by considering only one slice out of two and multiplied by a factor two the slice thickness. We compared the results with those obtained from the original shape, based on two criteria: the position of the skeleton and the estimation of the thickness.

10.2 Results

10.2.1 Estimation on the original atlas segmentation

The following section presents the results obtained from the original segmentation of the hippocampal ribbon.

The obtained skeleton is shown on figure 10.1. The first thing we can note is that the skeleton encodes the original shape of the hippocampus: it has the same topology (a sheet), and digitations in the head can be observed with the same precision than in the original volume. In figure 10.2, a cut at the level of the hippocampal body reveals the respective position of the skeleton and the original segmentation. We can observe that the skeleton



Figure 10.1: Top and bottom views of the hippocampal ribbon skeleton

fits correctly at the middle of the volume. The thickness along the hippocampal skeleton is depicted on figure 10.3. We can observe that, at the level of the head, the thickness is greater at the bottom of the digitations than at the top. Figures 10.4 and 10.5 respectively present the computed streamlines and thickness in a cut at the level of the hippocampal body.

10.2.2 2D/3D comparison

The method presented above can be applied to both 2D and 3D images. In the hippocampal body, if the images are acquired in a plane perpendicular to the long axis of the hippocampus, the z-coordinate of the vector field will be close to zero. When the slice thickness is very large compared to the in-plane resolution, we want to test if a 2D method can accurately estimate the position of the skeleton and the associated thickness.





Thus, we compared the result of the method computed in 2D slice by slice, with the result computed in 3D. We restricted the comparison to the hippocampal body, since the orientation of the head and tail do not allow a 2D approximation.

The 3D and 2D-skeleton are superposed in figure 10.6. The appareance of the 2D-skeleton is very similar to that of the 3D-skeleton. Indeed, the mean distance between points of the 2D-skeleton and the 3D-skeleton is 0.02 mm, while the correlation between thickness values of the two methods is 0.99. The difference between the two sets of thickness values can be visualized on figure 10.7.

10.2.3 Robustness to changes in slice thickness

Figure 10.8 shows the skeleton obtained from the subsampled volume (in blue), superimposed with the skeleton from the original volume (in yellow). We can see that the two skeletons have a similar shape and are very close to each other. In order to compare the estimated thickness values, we projected the thickness value at each vertex of the subsampled skeleton onto its closest vertex of the original skeleton. The difference between the two thickness maps can be seen in figure 10.9. The two thickness maps are very similar, especially in the body. The largest differences are located in the digitations, in particular in the tail of the hippocampus. This is due to the fact that, in this region, the digitations are approximately parallel to the XY plane. The high concordance between thickness maps was confirmed when



Figure 10.3: Thickness estimation plotted on the computed skeleton, based on the original segmentation of the postmortem atlas. The colorbar represents the range of thickness values in mm.



Figure 10.4: Computed streamlines in a cut at the level of the hippocampal body.



Figure 10.5: Computed thickness measures in a cut at the level of the hippocampal body. The colorbar represents the range of thickness values in mm.

we examined the correlations of the thickness values of the two experiments. Table 10.1 presents the correlation and the mean distance between the skeletons, in the head, the body, the tail, and in the whole hippocampus. One can observe very strong correlations between thickness estimations (between 0.94 and 0.99) and very low distances between skeletons (between 0.03mm and 0.05mm).

	Correlation	Mean Distance (mm)
Head	0.94	0.05
Body	0.99	0.03
Tail	0.94	0.05
H+B+T	0.95	0.04

Table 10.1: Correlation between thickness values and mean distance between skeletons computed from the original volume and those computed from the subsampled volume.



Figure 10.6: Superimposition of the skeleton and thickness maps obtained when the method was applied in 2D or 3D, in the body. The 3D skeleton is displayed in transparency. The colorbar represents the range of thickness values in mm.

10.3 Conclusion

In this chapter, we used the postmortem atlas to evaluate the thickness and skeleton estimation method that we proposed in the previous chapter. In particular, we studied its robustness to changes in slice thickness, by subsampling the quasi-isotropic atlas in the z direction. Thickness values computed from original and subsampled volumes were strongly correlated and skeletons were spatially very close. In the next chapters, we will apply our approach to in vivo data acquired at 7T.



Figure 10.7: Comparison between the thickness computed with the 2D and the 3D method, in the hippocampal body. Colors represent differences in thickness values in mm.



Figure 10.8: Superimposition of the skeleton obtained from the original volume (in yellow) and of the skeleton obtained from the subsampled volume (in blue).



Figure 10.9: Comparison of the estimated thickness on the original and sub-sampled volumes. Colors represent the difference between the two thickness maps.



TEMPLATE ESTIMATION AT THE GROUP LEVEL USING LARGE DEFORMATIONS AND CURRENTS

In chapter 9, we introduced a skeletonization and thickness estimation approach based on a variational formulation for modeling shapes. Our final objective is to be able to apply this approach to group studies to detect thickness and/or shape differences between populations of subjects. We want to perform analysis of both thickness data (projected onto the template) and deformation maps (moving each skeleton to the template). These two analysis can be seen as complementary because the skeleton encodes all morphological information not related to thickness. Before defining and estimating such statistical models, it is necessary to be first able to position the computed skeleton of each individual in a common template.

A very large number of deformation frameworks have been proposed in the field of medical imaging, mostly for the registration of images [Ashburner et al., 2007; Avants & Gee, 2004; Shen & Davatzikos, 2002]. A review of existing deformation frameworks is beyond the scope of this thesis. Among other possible choices, the Large Deformation Diffeomorphic Metric Mapping (LDDMM) framework [Dupuis et al., 1998; Trouvé, 1998] seems particularly adapted for our objective, for two main reasons. First, it provides smooth invertible deformations which are thought to be more consistent with the underlying anatomy. Second, it is particularly adapted to statistical analysis of deformations which are determined by initial momenta that live in a RKHS. Moreover, this deformation framework can be used for the registration of shapes modeled as currents [Vaillant & Glaunes, 2005; Glaunes et al., 2008; Durrleman et al., 2009]. The purpose of this chapter is therefore to introduce the LDDMM

11.1 Flows of diffeomorphisms for registration

11.1.1 Shapes modeled as currents

The definitions below come from [Durrleman et al., 2009].

Mathematically, a current is a continuous linear mapping $L_w(\omega)$ from a vector space W to \mathbb{R} , i.e. it is an application that integrates vector fields. The current of a surface S is the flux of a test vector field $\omega \in W$ across that surface. The shape of the surface S is uniquely characterized by the variations of the flux as the test vector field varies.

Given ω a 3D vector field in *W*, a surface *S* integrates ω thanks to the flux equation:

$$S(\omega) = \int_{S} \omega(x) (u \times v)(x) d\sigma(x)$$
(11.1)

where $(u\ddot{\imath}_{i}v)(x)$ is the normal of the surface at point *x*, (u, v) an orthonormal basis of its tangent plane at *x*, and $d\sigma$ the Lebesgue measure on the surface.

The element that makes this framework possible is to choose the vector space of the test vector fields W as the vector space generated by the convolutions between any square integrable vector field and a smoothing kernel K_W : W is a RKHS.

W is the dense span of basis vector fields of the form $\omega(x) = K_W(x, y)\beta$, for any vectors β . The kernel K_W defines an inner product in *W* that can be easily computed by:

$$\langle \omega(.), \nu(.) \rangle_W = \langle K_W(., x) \alpha, K_W(., y) \beta \rangle = \alpha^T K_W(x, y) \beta$$
(11.2)

A consequence of these properties is that the space of currents W^* (the dual space of W), is the dense span of the dual representations of the basis vectors $\omega(.)$, called Dirac delta currents $\delta_x^{\alpha}(\omega)$ and defined by:

$$\delta_x^{\alpha}(\omega) = \langle K_W(., x)\alpha, \omega(.) \rangle_w = \alpha^T \omega(x)$$
(11.3)

A Dirac delta current is an infinitesimal vector α that is concentrated at the spatial position *x*. In that way, the current of a surface *S* can be decomposed into an infinite set of Dirac delta currents defined at each point of the surface and orientated along the surface normal.

In our application, the surfaces are represented by discrete triangulated meshes. Their current representation \mathcal{T} is therefore given by the finite sum:

$$\mathcal{T}(\omega) = \sum_{k} \delta_{x_k}^{n_k}(\omega) \tag{11.4}$$

where x_k are the barycentres of the mesh faces and n_k their normal. Its dual representation ω is therefore given at any point x by the finite sum:

$$\omega(x) = \sum_{k} K_W(x, x_k) n_k \tag{11.5}$$

As currents are linear applications, they define a vector space on shapes. The addition of two currents is equivalent to the union of the two surfaces. By construction, the space of currents W^* is equipped with an inner-product. The distance between two shapes can therefore be computed as the norm of the difference of their currents. The space of currents thus enables us to compute mean, standard deviations and other descriptive statistics on shapes, without assuming any point correspondances between them.

11.1.2 Shape registration based on currents

The problem of shape registration may be formulated as the search of an "optimal" deformation (in a sense to be defined) which enables to minimize the dissimilarity between the deformed source shape and the target shape.

In the previous section, we showed how surfaces can be modeled as currents. The norm between currents provides a metric on the space of shapes. In the following, we will define a registration scheme, which is compatible with the framework based on currents.

11.1.3 Diffeomorphism-based registration

Once the measure of dissimilarity has been given, we have to define the class of deformations to be used for the registration. Several choices are possible. The deformations with the fewest degrees of freedom are the rigid-body transformations (translation and rotation) and scaling. These groups of linear transformations can be extended to the more general affine deformation group with 12 degrees of freedom. In these cases, optimizing a criterion over the whole space of possible transformations is particularly easy due to the small number of parameters to be optimized. However, these deformations are linear and, as such, may be unable to capture local variations of shapes. Therefore, we must enlarge the space of possible deformations to capture relevant anatomical variations.

The diffeomorphisms are the non-linear extension of the invertible linear transformations (isomorphisms). A diffeomorphism is a smooth mapping of the space into itself, invertible with smooth inverse. As non-linear deformations, they are particularly well suited to capture local smooth variations. The purpose of registration, here, is not to find a diffeomorphic deformation which perfectly aligns one shape onto another. Indeed, the inter-individual variability can involve changes which cannot be captured by diffeomorphisms. In this setting, the registration is a trade-off between the regularity of the deformation and the fidelity-todata.

Contrary to the linear transformations which have a finite dimensional parameterization, diffeomorphisms have an infinite number of degrees of freedom, and optimizing a registration criterion over the whole group of diffeomorphisms might not be possible. We can define smaller groups of diffeomorphisms, which still are of infinite dimension, but which allow to be processed via discrete parameterizations. The LDDMM framework is based on the group of diffeomorphisms [Dupuis et al., 1998; Trouvé, 1998] which is constructed via integration of time-varying vector fields which belong to RKHS. This framework has been developped for various kinds of data: images, landmarks, surfaces, tensor-valued images ...

11.2 Measure-based diffeomorphic matching of hippocampal skeletons

In order to perform morphometric analysis of the hippocampal substructures, we use nonrigid registration to position the computed skeleton of each individual in a common template. We choose to use the general framework of the Large Deformation Metric Mapping (LDDMM) theory [Trouvé, 1998] to model dense diffeomorphic transformations which, at the discrete level, are parametrized by a finite set of vectors, suitable for statistical analysis. We briefly sketch the mathematical model and the multi-subject registration procedure in this section.

11.2.1 Multi-subject registration

Let $S_i = \sum_k n_k \delta_{x_k}$ be the current representing the skeleton surface of the *i*-th individual. The multi-subject registration of sets S_i , $1 \le i \le N$ is defined as the minimizer of

$$J(\Phi_1, \dots, \Phi_N, S_{tpl}) = \sum_{i=1}^N \left\{ \lambda E_{Reg}(\Phi_i) + E_{Dist}(\Phi(S_i), S_{tpl}) \right\},$$
(11.6)

where each Φ_i is a diffeomorphic map in \mathbb{R}^3 ; S_{tpl} is the unknown template, E_{Reg} controls for smoothness of the map, and E_{Dist} measures the residual dissimilarity between $\Phi(S_i) = (\Phi(x_j^i))_{j=1}^{n_i}$ and the template. This template estimation approach is directly inspired from [Glaunes & Joshi, 2006].

It is beyond the scope of this thesis to develop the diffeomorphic model and the definition of $E_{Reg}(\Phi_i)$, and we refer the reader to Trouvé [1998]. In the following we focus on the definition of the dissimilarity measure E_{Dist} .

11.2.2 Dissimilarity measure between surfaces

We formally model the surfaces S_i as the sum $S_i = \sum_k n_k^i \delta_{x_k^i}$. These currents are then embedded into a Hilbert space structure which defines a scalar product and distances between any two surfaces. More precisely, the dissimilarity between the surfaces *S* and *T* is evaluated as the squared Hilbert distance between the associated currents, via the following formula:

$$E_{Dist}(S,T) = \sum_{k,l} n_k^S K_W(x_k^S, x_l^S) n_l^S - 2 \sum_{k,q} n_k^S K_W(x_k^S, x_q^T) n_q^T + \sum_{q,r} n_q^T K_W(x_q^T, x_r^T) n_r^T$$
(11.7)

where K_W is a specified positive kernel. In our experiment, we used $K_W(x, y) = \frac{1}{1 + \frac{(x-y)^2}{\sigma_W^2}}$,

with $\sigma_W > 0$.

11.2.3 Optimization technique

Optimization of 11.6 is performed using an alternating minimization process, which consists in optimizing separately on each map Φ_i , then on S_{tpl} , and looping this whole procedure until convergence. Optimization on Φ_i is a classical pairwise registration step between S_i and the template, and we refer to [Glaunes et al., 2004] for implementation details. Next, using our model of currents, optimization on the template is in fact straightforward because it simply consists in taking the average of the *N* mapped currents $\Phi_i(S_i)$: $S_{tpl} = \frac{1}{N} \sum_{i=1}^{N} \Phi_i(S_i)$. This means that the template is simply the union of the N surfaces, with a ponderation of $\frac{1}{N}$.

11.2.4 Choosing the right parameters

The performance of the multi-template registration method we described strongly depends on three main parameters, which are: the balance λ between regularity and data attachment terms, and the scale parameters σ_H and σ_I for the deformation model and the dissimilarity measure respectively. Heuristically, σ_H tells how the displacements $\Phi_i(x)$, $\Phi_i(y)$ of two given distant points x, y in 3-space are correlated, and should be set to some fraction of the typical size of the data. σ_I tells at which level of detail the sets of points forming the skeletons are compared via the dissimilarity measure. Since we want to take the full benefit from our high resolution data, we choose to set it to the size of the voxel. But since small values of the scale parameter increase the chance of the algorithm to get trapped in local minima, we use a multi-scale approach: σ_I is first set to a large value and decreased after each loop of the optimization procedure described earlier, finally reaching the desired value.

11.3 Conclusion

In this chapter, we have introduced an approach to estimate a template from a population of hippocampal skeletons. The approach is based on the LDDMM framework and models the surfaces as currents. The template estimation itself is directly inspired from [Glaunes & Joshi, 2006]. An alternative could be to use a "forward" scheme, proposed by [Durrleman et al., 2009], in which the individual surfaces are seen as deformations from the template, rather than defining the template as an average of deformed individuals. Finally, another interesting perspective would be to use a recently proposed approach [Durrleman et al., 2012] in which the template is defined as a single topologically-correct surface rather than as a collection. In the next chapter, we will apply the template estimation approach to a population of healthy controls and patients with temporal lobe epilepsy scanned at 7T.



APPLICATION TO IN-VIVO DATA

In this chapter, we apply the proposed shape models of the hippocampal ribbon to in vivo data. We studied nine healthy subjects and eight patients with temporal lobe epilepsy (TLE), acquired in vivo at 7T, as part of our collaboration with University of Minnesota (Tom Henry, Pierre-Francois Van de Moortele, Kamil Ugurbil). We first extracted the skeleton and computed the associated thickness in each subject. We then built a template of hippocampal skeletons at the group level based on the LDDMM framework. This allowed us to perform a preliminary analysis of the thickness of the hippocampal ribbon in temporal lobe epilepsy.

12.1 7T MRI acquisition and segmentation

Eight adult patients with TLE and nine healthy volunteers were studied. Each patient with TLE had undergone prior clinical 1.5- or 3-T MR imaging, which revealed unilateral hippocampal atrophy or T2 signal increases. Ictal video electroencephalographic recordings showed unilateral temporal lobe ictal onset pattern for each patient, thus the TLE group was divided in two categories: 5 have ictal onset on the left (Left-TLE) and 3 on the right (Right-TLE).

High-resolution oblique coronal 2D T2-weighted images were acquired on a 7T MRI scanner (Siemens, Erlangen, Germany), using a 16-channel head coil. Four to six slabs of 27 1mm-thick slices with 1mm gap were acquired, registered and averaged, in order to create a volume of 54 contiguous 1mm-thick slices with 0.25x0.25mm in-plane resolution, as described in [Henry et al., 2011]. The orientation for all high-resolution scans was set perpendicular to the long hippocampal axis.

Ammon's horn (CA-GM) was segmented in the body of the hippocampus by Marie Chupin, following the procedure described in 7. In order to obtain complete segmentations of the hippocampal ribbon, I segmented myself the subiculum in all subjects. Since manual segmentation of subregions is particularly time consuming, we could only obtain the segmentations in the hippocampal body.

12.2 Shape modeling and template estimation

The skeleton and thickness maps of each subject were extracted using the 3D method described in chapter 9. Then, we estimated a common template from the group of subjects, as described in chapter 9. We set the three main parameters as follows. We fixed the trade-off paramater λ to 10^{-5} . The value of the scale parameter σ_W was initially set at the maximal Hausdorff distance between skeletons. This value linearly decreased at each iteration until it reached the value of the slice thickness. The diffeomorphic model also requires to specify a kernel K_D . We chose it to be of the same type as K_W , and set the corresponding scale parameter σ_D to 5 mm, which is approximatively one fourth of the typical size of the data.

Four experiments were conducted. We estimated a template from the nine left hippocampi of the controls and the five left hippocampi of the TLE patients with ipsilateral ictal onset; this experiment will be referred as "Controls-L vs TLE-IL". We then repeated the procedure to estimate a template from the left hippocampi of the controls and the three left hippocampi of TLE patients with contralateral ictal onset, and refer this experiment as "Controls-L vs TLE-CL". Similarly, the two last experiments are referred as "Controls-R vs TLE-IR" and "Controls-R vs TLE-CR".

Thickness data was then projected onto the corresponding template by using Radial Basis Function interpolation. A traditional choice for the RBF function $\psi(r) = exp(-r^2/\sigma^2)$ (Gaussian RBF) or $\psi(r) = r^{2k} log(r)$ (thin plate spline RBF). Here, we used a RBF function with compact support firstly introduced by Wendland [Wendland, 1995]:

$$\psi^{s}(r) = (1 - \frac{r}{s})^{4}_{+} (4\frac{r}{s} + 1), \qquad (12.1)$$

where *s* is a scale parameter. ψ_s is C^2 on \mathbb{R} . The use of a function with compact support ensures locality of the interpolation. We used this interpolation method, with a scale parameter *s* fixed to 4, to project each mapped skeleton $\phi_i(S_i)$ to one of the surfaces of the optimal template. This enables us to vizualize the mean thickness of each group and observe if there are some differences between the different populations.

Thickness data of each individual was then projected onto one of the registered surfaces, and averaged at the group level. Due to the small number of subjects, we prefered not to perform statistical tests for assessing significance and only displayed the differences for visual assessment. The results presented here have to be interpreted as trends and would need to be confirmed in a larger population.

12.3 Results

We present in this section the results of the four experiments described above.

Figure 12.1 presents the results of the template estimation for left and right hippocampal ribbons. One can observe that all subjects are correctly coregistered.

Mean thickness across the whole hippocampal body in controls and TLE patients is shown on figures 12.2 and 12.3. We can observe that thickness tends to be smaller in patients than in controls; this difference being more pronounced ipsilaterally to the focus.

These global trends can be further studied at the local level: figures 12.4 to 12.7 present the thickness maps (thickness values at each vertex of the hippocampal body) of controls



Figure 12.1: Template estimation for the hippocampal ribbons of controls and TLE patients. Left: Hippocampal ribbons in native space. A color is assigned to each individual. Right: Registered ribbons.



Figure 12.2: Mean thickness of the left hippocampus (averaged across the hippocampal body) in controls and TLE patients



Figure 12.3: Mean thickness of right hippocampus (averaged across the hippocampal body) in controls and TLE patients



Figure 12.4: Thickness maps for Controls-L vs TLE-IL (Top and bottom views). The hippocampal head is at the bottom of the images.

and patients for the Controls-L vs TLE-IL, Controls-R vs TLE-IR, ,Controls-L vs TLE-CL and Controls-R vs TLE-CR experiments respectively. There is a quite clear trend of thinning ispilaterally to the seizure focus, in particular in left TLE patients.

12.4 Discussion

Our experiments demonstrate the feasibility of studying local thickness changes in the hippocampal ribbon in a group of patients studied in vivo at 7T. Our approach allows extracting



Figure 12.5: Thickness maps for Controls-R vs TLE-IR (Top and bottom views)



Figure 12.6: Thickness maps for Controls-L vs TLE-CL (Top and bottom views)



Figure 12.7: Thickness maps for Controls-R vs TLE-CR (Top and bottom views)

skeletons and computing local thickness measures, and building a template to study differences between populations.

We found a global trend of thinning in patients with temporal lobe epilepsy compared to healthy controls, this difference being more pronounced ispilaterally to the seizure focus. When studying local thickness, we could also observe local thinning ipsilaterally, in particular in left TLE patients. These results are preliminary and need to be confirmed in a larger group of patients. However, the detected thinning of the ipsilateral hippocampal ribbon could reflect hippocampal sclerosis. Hippocampal sclerosis is characterized histologically by pyramidal neuronal loss and reactive gliosis. Our approach could constitute a promising tool assess the spatial pattern of atrophy in the hippocampal subregions associated with hippocampal sclerosis. In the future, it would also be interesting to assess its potential to detect alterations in TLE patients with normal hippocampal volume, so-called "MRInegative".

Beyond epilepsy, this approach provides a new way to assess local alterations of the hippocampal ribbon in pathologies. For instance, in Alzheimer's disease, lesions are thought to predominate in the subiculum and in CA1. Measurement of local thinning could thus lead to more sensitive biomarkers of the disease. In addition to thickness, shape changes of the skeleton are also an interesting feature which could be studied using our model, by analyzing statistically the deformations of the skeletons to the template.

CONCLUSION

Shape analysis of the hippocampus is important for investigating its alterations in neurological and psychiatric disorders. MRI allows studying the morphology of the hippocampus in vivo. However, conventional imaging, performed at 1.5T or 3T, only allows visualizing the external border of the hippocampus and not its rich internal architecture. Recent developments at ultra high field (7T and higher) have allowed to distinguish in vivo the subregions of the hippocampal formation, opening fascinating perspectives for morphometry.

* *

This thesis was devoted to the development and application of hippocampal shape models, for both conventional and ultra high field MRI.

In the context of conventional MRI, we proposed an approach to automatically classify individual subjects based on hippocampal shape features. This approach was based on the combination of spherical harmonics and support vector machines. When applied to patients with Alzheimer's disease and mild cognitive impairment, it resulted in high sensitivity and specificity that were superior to that of hippocampal volumetry. However, when applied to a larger database (ADNI), the performances were lower, in particular compared to whole-brain methods. Several factors may explain these discordant results. First, ADNI is a multicenter database, which introduces variability in image quality and possibly in diagnosis as well. Second, many ADNI patients have vascular lesions indicating a more "mixed" pathology. Finally, we also actively collaborated to a study on Gilles de la Tourette syndrome. Using cortical and hippocampal morphometry, we were able to demonstrate that the different clinical presentations are associated with distinct anatomical changes.

The other part of this thesis was devoted to the development of shape models for hippocampal subregions studied at ultra-high field (7T and higher). First, we segmented a 3D atlas of hippocampal subregions with very high quasi-isotropic resolution. Then, we designed a shape model for the hippocampal ribbon. To that purpose, we propose an original variational approach for decomposing the ribbon into a skeleton and thickness measurement. This relies on the estimation of a smooth vector field, represented using RKHS, that goes through the ribbon. The approach provides a diffeomorphic flow through the surface and is applicable to both 2D and 3D. We validated the approach using both synthetic datasets and the aforementioned 3D postmortem atlas. We finally applied it to a group of healthy subjects and patients with temporal lobe epilepsy (TLE) scanned in vivo at 7T. To that purpose, we created a template of hippocampal skeletons at the group level using Large Deformation Diffeomorphic Metric Mapping (LDDMM) and the representation of surfaces as currents. Our approach allowed detecting thinning of the hippocampal ribbon in TLE patients ipsilaterally to the focus. Even though these results are preliminary, they indicate that this new shape model could be a promising approach to study alterations of hippocampal subregion with very high spatial resolution.

* *

There are various perspectives to this thesis.

The application of the hippocampal ribbon shape model to in vivo data is preliminary. A first perspective is to apply the shape model to the whole hippocampal ribbon (head, body and tail) and not only to the body. This has not been possible within this thesis because manual segmentation of 7T data is particularly time-consuming. This would require either to dedicate more operator time to manual segmentation or to design an automatic segmentation approach. The latter has been recently started by Linda Marrakchi, who is a postdoc in our group. Besides, it is important to study a larger population of subjects, in order to confirm our preliminary results. This would allow performing a statistical analysis of shape differences. First, our approach could be combined to vertex-wise statistical tests to detect local thinning or thickening of the ribbon. Second, the skeleton seems to be an ideal object to study shape independently of local thickness. This could be done by using statistics on the deformations that map individual skeletons to the template, and, more specifically, statistics on the initial momenta.

There are several methodological perspectives for this shape model. First, it would be interesting to extend this model to handle other structures of the hippocampal formation, such as the hilum of the dentate gyrus, or other neighbouring structures, such as the entorhinal cortex. Altogether, this could provide a comprehensive morphometric assessment of the medial temporal lobe at very high spatial resolution. Another important issue is to be able to transfer at least a part of these very detailed models to conventional images acquired at 3T. Indeed, 7T MRI is not yet widely accessible which limits the application to large patient series. This will require to design registration procedures that could match 7T atlases with individual anatomy imaged at 3T while preserving the underlying anatomical organization.

The shape model of the hippocampal ribbon seems an interesting tool to investigate both anatomical variability in healthy subjects and alterations in disease. Indeed, the hippocampal ribbon exhibits variable patterns of folding in healthy subjects, the most striking feature being probably the digitations. However, this variability has not yet been extensively studied, mainly because these features were not visible in vivo. Statistical analysis of deformations could provide a more comprehensive view of this variability. The shape model could also prove useful to study neurodegenerative and neurodevelopmental pathologies. In Alzheimer's disease, it could be used to detect local thinning of the ribbon, possibly yielding more sensitive biomarkers. In developmental disorders, it could be used to study atypical folding patterns of the hippocampal ribbon.



AUTOMATIC CLASSIFICATION OF PATIENTS WITH ALZHEIMER'S DISEASE FROM STRUCTURAL MRI: A COMPARISON OF TEN METHODS USING THE ADNI DATABASE

This appendix reproduces the paper Cuingnet et al. [2011] (see chapter 5).

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Supplement

Automatic classification of patients with Alzheimer's disease from structural MRI: A comparison of ten methods using the ADNI database

Rémi Cuingnet ^{a,b,c,d,*}, Emilie Gerardin ^{a,b,c}, Jérôme Tessieras ^{a,b,c}, Guillaume Auzias ^{a,b,c}, Stéphane Lehéricy ^{a,b,c,e}, Marie-Odile Habert ^{d,f}, Marie Chupin ^{a,b,c}, Habib Benali ^d, Olivier Colliot ^{a,b,c} and The Alzheimer's Disease Neuroimaging Initiative ¹

^a UPMC Université Paris 6, UMR 7225, UMR_S 975, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (CRICM), Paris, F-75013, France

^b CNRS, UMR 7225, CRICM, Paris, F-75013, France

^c Inserm, UMR_S 975, CRICM, Paris, F-75013, France

^d Inserm, UMR_S 678, LIF, Paris, F-75013, France

Contro, Guine, Goine, Jordan, J. Carlos, J. Carlos, J. Carlos, J. Carlos, J. Carlos, C. Carlos,

^f AP-HP, Department of Nuclear Medicine, Groupe hospitalier Pitié-Salpêtrière, Paris, F-75013, France

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ABSTRACT

Recently, several high dimensional classification methods have been proposed to automatically discriminate between patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) and elderly controls (CN) based on T1-weighted MRI. However, these methods were assessed on different populations, making it difficult to compare their performance. In this paper, we evaluated the performance of ten approaches (five voxel-based methods, three methods based on cortical thickness and two methods based on the hippocampus) using 509 subjects from the ADNI database. Three classification experiments were performed: CN vs AD, CN vs MCIc (MCI who had converted to AD within 18 months, MCI converters - MCIc) and MCIc vs MCInc (MCI who had not converted to AD within 18 months, MCI non-converters - MCInc). Data from 81 CN, 67 MCInc, 39 MCIc and 69 AD were used for training and hyperparameters optimization. The remaining independent samples of 81 CN, 67 MCInc, 37 MCIc and 68 AD were used to obtain an unbiased estimate of the performance of the methods. For AD vs CN, whole-brain methods (voxel-based or cortical thicknessbased) achieved high accuracies (up to 81% sensitivity and 95% specificity). For the detection of prodromal AD (CN vs MCIc), the sensitivity was substantially lower. For the prediction of conversion, no classifier obtained significantly better results than chance. We also compared the results obtained using the DARTEL registration to that using SPM5 unified segmentation. DARTEL significantly improved six out of 20 classification experiments and led to lower results in only two cases. Overall, the use of feature selection did not improve the performance but substantially increased the computation times.

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Introduction

Alzheimer's disease (AD) is the most frequent neurodegenerative dementia and a growing health problem. Definite diagnosis can only be made postmortem, and requires histopathological confirmation of amyloid plaques and neurofibrillary tangles. Early and accurate

E-mail address: remi.cuingnet@gmail.com (R. Cuingnet).

diagnosis of Alzheimer's Disease (AD) is not only challenging, but is crucial in the perspective of future treatments. Clinical diagnostic criteria are currently based on the clinical examination and neuropsychological assessment, with the identification of dementia and then of the Alzheimer's phenotype (Blennow et al., 2006). Patients suffering from AD at a prodromal stage are, mostly, clinically classified as amnestic mild cognitive impairment (MCI) (Petersen et al., 1999; Dubois and Albert, 2004), but not all patients with amnestic MCI will develop AD. Recently, more precise research criteria were proposed for the early diagnostic of AD at the prodromal stage of the disease (Dubois et al., 2007). These criteria are based on a clinical core of early episodic memory impairment and the presence of at least one additional supportive feature including abnormal MRI and PET neuroimaging or abnormal cerebrospinal fluid amyloid and tau biomarkers (Dubois et al., 2007). Neuroimaging therefore adds a positive predictive value to the diagnosis and includes measurements

^{*} Corresponding author. CRICM, Equipe Cogimage (ex LENA), Hôpital de la Pitié-Salpêtrière, 47, boulevard de l'Hôpital, 75651 Paris Cedex 13, France.

¹ Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. ADNI investigators include (complete listing available at http://www.loni.ucla.edu/ADNI/Collaboration/ADNI Author ship list.pdf).

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using structural MRI to assess medial temporal lobe atrophy and positron emission tomography using fluorodeoxyglucose (FDG) or amyloid markers (Fox and Schott, 2004; Jagust, 2006).

Many group studies based on volumetric measurements of regions of interest (ROI) (Convit et al., 1997, 2000; Jack et al., 1997,1998; Juottonen et al., 1998; Laakso et al., 1998, 2000; Busatto et al., 2003; Xu et al., 2000; Good et al., 2002; Chételat and Baron, 2003; Rusinek et al., 2004; Tapiola et al., 2008), voxel-based morphometry (Good et al., 2002; Busatto et al., 2003; Karas et al., 2003, 2004; Chételat et al., 2005; Whitwell et al., 2007, 2008) or group comparison of cortical thickness (Thompson et al., 2001, 2003, 2004; Lerch et al., 2005, 2008; Bakkour et al., 2009, Dickerson et al., 2009; Hua et al., 2009; McDonald et al., 2009) have shown that brain atrophy in AD and prodromal AD is spatially distributed over many brain regions including the entorhinal cortex, the hippocampus, lateral and inferior temporal structures, anterior and posterior cingulate. However these analyses measure group differences and thus are of limited value for individual diagnosis.

Advances in statistical learning with the development of new machine learning algorithms capable of dealing with high dimensional data, such as the support vector machine (SVM) (Vapnik, 1995; Shawe-Taylor and Cristianini, 2000; Schölkopf and Smola, 2001), enable the development of new diagnostic tools based on T1weighted MRI. Recently, several approaches have been proposed to automatically classify patients with AD and/or MCI from anatomical MRI (Fan et al., 2005, 2007, 2008a,b; Colliot et al., 2008; Davatzikos et al., 2008a,b; Klöppel et al., 2008; Vemuri et al., 2008; Chupin et al., 2009a,b; Desikan et al., 2009; Gerardin et al., 2009; Hinrichs et al., 2009; Magnin et al., 2009; Misra et al., 2009; Querbes et al., 2009). These approaches could have the potential to assist in the early diagnosis of AD. These approaches can roughly be grouped into three different categories, depending on the type of features extracted from the MRI (voxel-based, vertex-based or ROI-based). In the first category, the features are defined at the level of the MRI voxel. Specifically, the features are the probability of the different tissue classes (grey matter, white matter and cerebrospinal fluid) in a given voxel (Lao et al., 2004; Fan et al., 2007, 2008a,b; Davatzikos et al., 2008a,b; Klöppel et al., 2008; Vemuri et al., 2008; Hinrichs et al., 2009; Magnin et al., 2009; Misra et al., 2009). Klöppel et al. (2008) directly classified these features with an SVM. All other methods first reduce the dimensionality of the feature space relying on different types of features extraction, agglomeration and/or selection methods. Vemuri et al. (2008) used smoothing, voxel-downsampling, and then a feature selection step. Another solution is to group voxels into anatomical regions through the registration of a labeled atlas (Lao et al., 2004; Ye et al., 2008; Magnin et al., 2009). However, this anatomical parcellation may not be adapted to the pathology. In order to overcome this limitation, Fan et al. (2007) have proposed an adaptive parcellation approach in which the image space is divided into the most discriminative regions. This method has been used in several studies (Davatzikos et al., 2008a,b; Fan et al., 2008a,b; Misra et al., 2009). In the second category, the features are defined at the vertex-level on the cortical surface (Desikan et al., 2009; Querbes et al., 2009). The methods of the third category include only the hippocampus. Their approach is based on the analysis of the volume and/or shape of the hippocampus (Colliot et al., 2008, Chupin et al., 2009a,b; Gerardin et al., 2009).

These approaches achieve high accuracy (over 84%). However, they were evaluated on different study populations, making it difficult to compare their respective discriminative power. Indeed, many factors such as degree of impairment, age, gender, genotype, educational level and MR image quality perceptibly affect the evaluation of the prediction accuracy. This variability between evaluations is increased for statistical reasons when the number of subjects is small. Therefore a meta-analysis would be of limited value to compare the prediction accuracies of different methods.

The goal of this paper was to compare different methods for the classification of patients with AD based on anatomical MRI, using the

same study population. To that purpose, we used the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Ten methods were evaluated. We tested five voxel-based approaches: a direct approach (Klöppel et al., 2008), an approach based on a volume of interest (Klöppel et al., 2008), an atlas-based approach (Magnin et al, 2009) and the approaches proposed by Vemuri et al. (2008) and Fan et al. (2008a,b) respectively. In order to assess the influence of the registration step and the features used on the classification accuracies, these latter methods were tested with two different registration steps: SPM5 (Ashburner and Friston, 2005) and DARTEL (Ashburner, 2007) and also with either only the grey matter (GM) probability maps or all the tissues probability maps including also white matter (WM) and cerebrospinal fluid (CSF). Three cortical approaches were evaluated as well: a direct one similar to (Klöppel et al., 2008), an atlas based one and an approach using only the regions found in (Desikan et al., 2009). Two methods respectively based on the volume (Colliot et al., 2008, Chupin et al., 2009a,b) and the shape (Gerardin et al., 2009) of the hippocampus were also tested.

Materials

Data

Data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (http:// www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

MRI acquisition

The MR scans are T1-weighted MR images. MRI acquisition had been done according to the ADNI acquisition protocol in (Jack et al., 2008). For each subject, we used the MRI scan from the baseline visit when available and from the screening visit otherwise. We only used images acquired at 1.5 T. To enhance standardization across sites and platforms of images acquired in the ADNI study, pre-processed images that have undergone some post-acquisition correction of certain image artifacts are available (Jack et al., 2008). We used those corrected in image geometry for gradient nonlinearity and corrected for intensity non-uniformity due to non-uniform receiver coil sensitivity. The image geometry correction was the 3D gradwarp correction (Hajnal et al., 2001; Jovicich et al. 2006). The B1 non-uniformity correction is detailed in Narayana et al. (1988). These two preprocessing steps can be performed directly on the MRI console and thus seem feasible in clinical routine. All subjects were scanned twice at each visit. As explained in Jack et al. (2008), MR scans were graded qualitatively by the ADNI investigators of the ADNI MRI quality control center at the Mayo Clinic for artifacts and general image quality. Each scan was graded on several separate criteria: blurring/ghosting, flow artifact, intensity and homogeneity, signal-to-noise ratio (SNR), susceptibility artifacts, and gray-white/cerebrospinal fluid contrast. For each subject, we used the MRI scan which was considered as the "best" quality scan by the ADNI investigators. In the description of the ADNI methods (http:// www.loni.ucla.edu/ADNI/Data/ADNI_Data.shtml), the "best" quality

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image is the one which was used for the complete pre-processing steps. We thus used the images which had been selected for the complete preprocessing pipeline. No other exclusion criteria based on image quality were applied. The identification numbers of the images used in this study are reported in Tables S2 to S9.

Participants

The criteria used for the inclusion of participants were those defined in the ADNI protocol (described in details at http://www.adni-info.org/ Scientists/AboutADNI.aspx#). Enrolled subjects were between 55 and 90 (inclusive) years of age, had a study partner able to provide an independent evaluation of functioning, and spoke either English or Spanish. All subjects were willing and able to undergo all test procedures including neuroimaging and agreed to longitudinal follow up. Specific psychoactive medications were excluded. General inclusion/ exclusion criteria were as follows: control subjects (CN) had MMSE scores between 24 and 30 (inclusive), a CDR (Clinical Dementia Rating) (Morris, 1993) of zero. They were non-depressed, non MCI, and nondemented. MCI subjects had MMSE scores between 24 and 30 (inclusive), a memory complaint, had objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II (Wechsler, 1987), a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. AD patients had MMSE scores between 20 and 26 (inclusive), CDR of 0.5 or 1.0, and met NINCDS/ADRDA criteria for probable AD (McKhann et al., 1984).

We selected all the subjects for whom preprocessed images were available. The identification numbers of the subjects used in this study are reported in Tables S2 to S9. As a result, 509 subjects were selected: 162 cognitively normal elderly controls (CN) (76 males, 86 females, $age \pm SD = 76.3 \pm 5.4$ years, range = 60–90 years, and mini-mental score (MMS) = 29.2 ± 1.0 , range = 25-30), 137 patients with AD (67 males, 70 females, age \pm SD = 76.0 \pm 7.3 years, range = 55–91 years, and MMS = 23.2 ± 2.0 , range = 18-27), 76 patients with MCI who had converted to AD within 18 months (MCIc) (43 males, 33 females, age \pm $SD = 74.8 \pm 7.4$ years, range = 55–88 years, and MMS = 26.5 ± 1.9 , range = 23-30) and 134 patients with MCI who had not converted to AD within 18 months (MCInc) (84 males, 50 females, age \pm SD = 74.5 \pm 7.2 years, range = 58-88 years, and MMS = 27.2 ± 1.7 , range = 24-30). We did not consider MCI patients who had been followed less than 18 months and had not converted within this time frame. The 509 images came from 41 different centers.

To assess differences in demographic and clinical characteristics between groups, we used Student's t-test for age and MMS and Pearson's chi-square test for gender. Significance level was set at 0.05. No significant differences were found except for the MMS between controls and patients (AD or MCIc, p < 0.0001).

In order to obtain unbiased estimates of the performances, the set of participants was then randomly split up into two groups of the same size: a training set and a testing set. The algorithms were trained on a training set and the measures of the diagnostic sensitivity and specificity were carried out with an independent test set. The division process preserved the age and sex distribution.

Demographic characteristics of the studied population selected from the ADNI database are presented in Table 1.

Methods

Classification experiments

Three classification experiments were performed to compare the different approaches. The first one is the classification between CN subjects and patients with probable AD and is referred to as "CN vs AD" in the following. The second one is the classification between CN subjects and MCI converters and is referred to as "CN vs MCIc". It corresponds to the detection of patients with prodromal AD as defined by Dubois and Albert (2004). Indeed, MCI patients who will convert to AD are, at baseline, patients with incipient AD but non-demented, i.e. patients with prodromal AD. The third one is the classification MCInc versus MCIc and is referred to as "MCInc vs MCIc". It corresponds to the prediction of conversion in MCI patients.

Classification methods

The different approaches we compared can be grouped into three categories with respect to the features used for the classification. In the first category, the features are defined at the level of the MRI voxel. Specifically, the features are the probability of the different tissue classes (GM, WM and CSF) in a given voxel. In the second category, the features are defined at the vertex-level on the cortical surface. Specifically, the features are the cortical thickness at each vertex of the cortex. The methods of the third category include only the hippocampus.

These methods are summarized in Table 2 and briefly presented in the following paragraphs.

First category: voxel-based segmented tissue probability maps

The features of the methods of the first category were computed as follows. All T1-weighted MR images were spatially normalized and segmented into GM, WM and CSF using the SPM5 (Statistical Parametric Mapping, London, UK) unified segmentation routine (Ashburner and Friston, 2005) with the default parameters. These maps constitute a first set of tissue probability maps and will be referred to respectively as SPM5_GM, SPM5_WM and SPM5_CSF.

To evaluate the impact of the registration step on the classification accuracy, the GM and WM probability maps in native space segmented by the SPM5 unified segmentation routine were also normalized to the population template generated from all the images, using the DARTEL diffeomorphic registration algorithm (Ashburner, 2007) with the default parameters. The obtained transformations were applied to the GM, WM and CSF tissue maps. These maps compose a second set of

Table 1

Demographic characteristics of	f the studied population (from the ADNI database). Val	lues are indicated as mea	$n \pm standard-deviation [range].$
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Group	Diagnostic	Number	Age	Gender	MMS	# Centers
Whole set	CN	162	76.3±5.4 [60-90]	76 M/86 F	29.2 ± 1.0 [25–30]	40
	AD	137	76.0±7.3 [55–91]	67 M/70 F	23.2±2.0 [18-27]	39
	MCIc	76	74.8±7.4 [55-88]	43 M/33 F	26.5±1.9 [23-30]	30
	MCInc	134	74.5±7.2 [58-88]	84 M/50 F	27.2±1.7 [24-30]	36
Training set	CN	81	76.1±5.6 [60-89]	38 M/43 F	29.2 ± 1.0 [25–30]	35
	AD	69	75.8±7.5 [55-89]	34 M/35 F	23.3 ± 1.9 [18–26]	32
	MCIc	39	74.7±7.8 [55-88]	22 M/17 F	26.0±1.8 [23-30]	21
	MCInc	67	74.3±7.3 [58-87]	42 M/25 F	27.1±1.8 [24-30]	30
Testing set	CN	81	76.5±5.2 [63-90]	38 M/43 F	29.2 ± 0.9 [26-30]	35
-	AD	68	76.2±7.2 [57–91]	33 M/35 F	23.2±2.1 [20-27]	33
	MCIc	37	74.9±7.0 [57-87]	21 M/16 F	26.9±1.8 [24-30]	24
	MCInc	67	74.7±7.3 [58-88]	42 M/25 F	27.3 ± 1.7 [24–30]	31

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Table 2

Summary of the approaches tested in this study.

Features		Segmentation registration	Tissues probability maps	Classifier	Method #	Method's name
Voxel-segmented tissue probability maps	Direct	DARTEL	GM	Linear SVM	1.1.1 a	Voxel-Direct-D-gm
			GM + WM + CSF	Linear SVM	1.1.1 b	Voxel-Direct-D-all
		SPM5	GM	Linear SVM	1.1.2 a	Voxel-Direct-S-gm
			GM + WM + CSF	Linear SVM	1.1.2 b	Voxel-Direct-S-all
	Direct VOI	DARTEL	GM	Linear SVM	1.2.1 a	Voxel-Direct_VOI-D-gm
			GM + WM + CSF		1.2.1 b	Voxel-Direct_VOI-D-all
		SPM5	GM	Linear SVM	1.2.2 a	Voxel-Direct_VOI-S-gm
			GM + WM + CSF	Linear SVM	1.2.2 b	Voxel-Direct_VOI-S-all
	STAND-score	DARTEL	GM	Linear SVM	1.3.1 a	Voxel-STAND-D-gm
			GM + WM + CSF		1.3.1 b	Voxel-STAND-D-all
		SPM5	GM + WM + CSF	Linear SVM	1.3.2 a	Voxel-STAND-S-gm
				Linear SVM	1.3.2 b	Voxel-STAND-S-all
		SPM5 custom template	GM	Linear SVM	1.3.3 a	Voxel-STAND-Sc-gm
			GM + WM + CSF	Linear SVM	1.3.3 b	Voxel-STAND-Sc-all
	Atlas	DARTEL	GM	Linear SVM	1.4.1 a	Voxel-Atlas-D-gm
			GM + WM + CSF	Linear SVM	1.4.1 b	Voxel-Atlas-D-all
		SPM5	GM	Linear SVM	1.4.2 a	Voxel-Atlas-S-gm
			GM + WM + CSF	Linear SVM	1.4.2 b	Voxel-Atlas-S-all
	COMPARE	DARTEL	GM	Linear SVM	1.5.1 a	Voxel-COMPARE-D-gm
			GM + WM + CSF	Linear SVM	1.5.1 b	Voxel-COMPARE-D-all
		SPM5	GM	Gaussian SVM	1.5.2 a	Voxel-COMPARE-S-gm
			GM + WM + CSF	Gaussian SVM	1.5.2 b	Voxel-COMPARE-S-all
Cortical thickness	Direct	Freesurfer	-	Linear SVM	2.1	Thickness-Direct
	Atlas	Freesurfer	-	Linear SVM	2.2	Thickness-Atlas
	ROI	Freesurfer	-	Logistic Reg.	2.3	Thickness-ROI
Hippocampus	Volume	Freesurfer	-	Parzen	3.1.1	Hippo-Volume-F
	Volume	SACHA	-	Parzen	3.1.2	Hippo-Volume-S
	Shape	SACHA	-	Linear SVM	3.2	Hippo-Shape

tissue probability maps and will be referred to respectively as DARTEL_GM, DARTEL_WM and DARTEL_CSF. Some papers used only GM maps while others included all three tissues. In our experiments, we systematically evaluated the added value of WM and CSF maps by comparing the classification obtained with only GM to that obtained with all three classes. All maps were then modulated to ensure that the overall tissue amount remains constant. No spatial smoothing was performed, unless when otherwise specified.

The different methods of this category differ by the way the features are extracted and/or selected from the voxel probability maps. This is detailed in the following paragraphs.

Direct

The simplest approach consists in considering the voxels of the tissue probability maps directly as features in the classification. This type of approach is referred to as "*Voxel-Direct*" in the following. Such an approach was proposed by Klöppel et al. (2008) with two different versions: one is based on whole brain datasets and the other includes only data from a volume of interest (VOI) located in the anterior medial temporal lobe, including part of the hippocampus. This volume of interest was defined as two rectangular cuboids centered on x = -17, y = -8, z = -18 and x = 16, y = -9, z = -18 in the MNI space. Their dimensions were 12 mm, 16 mm and 12 mm in the *x*, *y* and *z* directions respectively. The latter method will be referred to as "*Voxel-Direct_VOI*". In their paper, they used only DARTEL_GM maps. Here, we will test all approaches with the following sets of probability maps: SPM5_GM only, SPM5_GM and SPM5_WM and SPM5_CSF, DARTEL_GM only, DARTEL_GM, and DARTEL_WM and DARTEL_CSF.

STAND-score

Vemuri et al. (2008) proposed an approach called the STAND score, in which the dimensionality is reduced by a sequence of feature aggregation and selection steps. First, the tissue probability maps were smoothed and down-sampled by averaging. Then, voxels that contained less than 10% tissue density values and CSF in half or more of the images were not considered for further analysis. A feature selection step was then carried out. First, a linear SVM was applied for each tissue class, which attributes a weight to each feature. Only features of which weights are consistent with increased neurodegeneration in the pathological group were kept. Then a second feature selection step was performed on the remaining features. To ensure spatial consistency, neighboring voxels of the voxels selected so far were also selected. The features from the different tissue classes were concatenated and then used in the classification. This approach is referred to as "*Voxel-STAND*" in the following. In their paper, the features used for this approach were the GM, WM and CSF tissue probability maps segmented and registered with the SPM5 unified segmentation routine using a customized tissue probability maps. Thus we also tested the classification with customized tissue probability maps.

Atlas based

Another approach consists in grouping the voxels into anatomical regions using a labeled atlas. This type of approach is used in Lao et al. (2004); Magnin et al. (2009). Each tissue probability map in the stereotaxic space was parceled into 116 regions of interest (ROI) using the AAL (Automatic Anatomical Labeling) atlas (Tzourio-Mazoyer et al., 2002). In each ROI, we computed the mean tissue probability and used these values as features in the classification. Such an approach will be referred to as "*Voxel-Atlas*". Note that the AAL is a predefined anatomical atlas, which has not been specifically designed for studying patients with AD; its areas thus do not necessarily represent pathologically homogeneous regions.

COMPARE

Instead of using a predefined atlas, Fan et al. (2007, 2008a,b) proposed a parcellation that is adapted to the pathology. The thorough explanation of the method is in Fan et al. (2007). Very briefly, the concept of COMPARE is to create homogeneously discriminative regions. In these regions, the voxel values are aggregated to form the features of the classification. Feature selection steps are then performed to identify the most discriminative regions. In the following, we refer to this approach as "*Voxel-COMPARE*". We used the COMPARE software freely available on request for download online (https://www.rad. upenn.edu/sbia/software/index.html).

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Second category: cortical thickness

In this second category, the features are the cortical thickness values at each vertex of the cortical surface. Cortical thickness represents a direct index of atrophy and thus is a potentially powerful candidate to assist in the diagnosis of AD (Thompson et al., 2001, 2003, 2004; Lerch et al., 2005, 2008; Bakkour et al., 2009; Dickerson et al., 2009; Hua et al., 2009; McDonald et al., 2009). Cortical thickness measures were performed with the FreeSurfer image analysis suite (Massachusetts General Hospital, Boston, MA), which is documented and freely available for download online (http://surfer.nmr.mgh. harvard.edu/). The technical details of this procedure are described in Sled et al. (1998), Dale et al. (1999), Fischl et al. (1999a,b) and Fischl and Dale (2000). All the cortical thickness maps were registered onto the default FreeSurfer common template. Four subjects were not successfully processed by the FreeSurfer pipeline. Those subjects are marked by an asterisk in Tables S2 to S9. They could thus not be classified with the SVM and were excluded from the training set. For the testing set, the subjects were considered as 50% misclassified.

Direct

As in Klöppel et al. (2008) for voxel-based maps, the simplest way consists in considering cortical thickness values at every vertex directly as features in the classification with no other preprocessing step. This approach is referred to as "*Thickness-Direct*" in the following.

Atlas based

As in the voxel-based case, we also tested an approach where vertices are grouped into anatomical regions using an atlas. Such approach is used in (Querbes et al., 2009; Desikan et al., 2009). The cortical parcellation was carried out with the cortical atlas of (Desikan et al., 2006). The atlas is composed of 68 gyral based ROIs. In each ROI, we computed the mean cortical thickness and used these values as features in the classification. This approach is referred to as "*Thickness-Atlas*" in the following.

ROI

Desikan et al. (2009) parcellated the brain into neocortical and non-neocortical ROIs by wrapping an anatomical atlas (Desikan et al., 2006). They studied the discriminative power for CN vs MCIc of the mean thickness (neocortical regions) and the volume (both neocortical and non-neocortical regions). For their analysis, the mean thickness and the volumes of the right and the left hemispheres, for each ROI, were added together. The volumes were corrected using estimate of the total intracranial volume.

Their study was carried out on a cohort of 97 participants selected from the Open Access Series of Imaging Studies (OASIS) database (Marcus et al., 2007). They found out that, with a logistic regression analysis, the best set of discriminator was: the entorhinal cortex thickness, the supramarginal gyrus thickness and the hippocampal volume. They used these features with a logistic regression to classify CN and MCIc and to classify CN and AD. Therefore, in this approach, we used only these three features for the classification. This approach is referred to as "*Thickness-ROI*" in the following.

Third category: hippocampus

Finally, we tested the discriminative power of methods which consider only the hippocampus and not the whole brain or the whole cortex as in the two first categories. The hippocampus is affected at the earliest stages of the disease and has thus been used as a marker of early AD in a vast number of studies.

Here, the segmentation of the hippocampus was performed using SACHA, a fully automatic method we previously developed (Chupin et al., 2007, 2009a). This approach has been shown to be competitive with manual tracing for the discrimination of patients with AD and

MCI (Colliot et al., 2008; Chupin et al., 2009b). This approach segments both the hippocampus and the amygdala simultaneously based on competitive region-growing between these two structures. It includes prior knowledge on the location of the hippocampus and the amygdala derived from a probabilistic atlas and on the relative positions of these structures with respect to anatomical landmarks which are automatically identified.

We also evaluated the hippocampal volume obtained with the FreeSurfer image analysis suite.

Volume

We first tested the classification accuracy obtained when the only feature is the hippocampal volume. For each subject, we computed the volume of the hippocampi. Volumes were normalized by the total intracranial volume (TIV) computed by summing SPM5 segmentation maps of grey matter, white matter, and cerebrospinal fluid (CSF), inside a bounding box defined in standard space to obtain a systematic inferior limit. For more robustness with respect to segmentation errors, left and right volumes were averaged. The thorough explanation of the method is in (Chupin et al., 2007, 2009a,b). This approach is referred to as "*Hippo-Volume-S*" in the following.

We also evaluated this approach with the hippocampal volume obtained with the FreeSurfer image analysis suite and corrected with the total intracranial volume also obtained with obtained with FreeSurfer. This approach will be referred to as "*Hippo-Volume-F*".

Shape

We then tested an approach in which the features describe the hippocampal shape (Gerardin et al., 2009). Each hippocampus was described by a series of spherical harmonics (SPHARM) to model the shape of the segmented hippocampi. The classification features were based on the SPHARM coefficients. Specifically, each subject was represented by two sets (one for each hippocampus) of threedimensional SPHARM coefficients. The SPHARM coefficients were computed using the SPHARM-PDM (Spherical Harmonics-Point Distribution Model) software developed by the University of North Carolina and the National Alliance for Medical Imaging Computing (http://www. namic.org/Wiki/index.php/Algorithm:UNC:Shape_Analysis). In the original paper by our group describing this method (Gerardin et al., 2009), we used a feature selection step because the subjects groups were much smaller (less than 30 subjects in each group). When the number of subjects is small, the classifier can be more sensitive to uninformative features. In the present study, the number of subjects was larger and thus a feature selection step is less necessary and increases the risk of overfitting. We thus chose to avoid this selection step. We also tested the procedure with the selection step but it did not lead to further improvement in this study. Moreover, the degree of the SPHARM decomposition was set at four. Four subjects were not successfully processed by the SPHARM pipeline. Those subjects are marked by a dagger in Tables S2 to S9. They could thus not be classified with the SVM and were excluded from the training set. For the testing set, those subjects were considered as 50% misclassified. This approach is referred to as "Hippo-Shape" in the following.

Classification using SVM

Classifiers

A support vector machine is a supervised learning method. In brief: given a training set of size *K*: $(x_k, y_k)_{k=1...k}$, where x_k in \mathbf{R}^d are observations, and y_k in {-1,1} are corresponding labels, SVMs search for the optimal margin hyperplane (OMH) separating groups, i.e. the hyperplane for which the margin between groups is maximal. More details on SVM can be found in (Vapnik, 1995; Shawe-Taylor and Cristianini, 2000, 2004; Schölkopf and Smola, 2001). We used a linear C-SVM for all the approaches except COMPARE (Fan et al., 2007) for

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which a non-linear C-SVM with a Gaussian kernel was used. The SVM implementation relied on the LIBSVM Library (Chang and Lin, 2001).

The dimension of the features of the approach *Hippo-Volume* is only one. Therefore a much simpler classifier can be used with no hyperparameter: each participant is assigned to the closest group. Specifically, if S_1 and S_2 are two groups of participants with respective centers of mass defined as m_1 and m_2 , a new individual with hippo-campus volume x is assigned to the closest group according to its Euclidean distance to the center of mass. This is a Parzen window classifier with the linear kernel and assuming a prevalence of 50% (Shawe-Taylor and Cristianini, 2004).

As in (Desikan et al., 2009) a logistic regression is used instead of a SVM, the classification step of *Thickness-ROI* was also based on a logistic regression.

Evaluation

In order to obtain unbiased estimates of the performances, the set of participants was randomly split into two groups of the same size: a training set and a testing set. The division process preserves the age and sex distribution. The training set was used to determine the optimal values of the hyperparameters of each method and to train the classifier. The testing set was then only used to evaluate the classification performances. The training and testing sets were identical for all methods, except for those four cases for which the cortical thickness pipeline failed and those other four for which the SPHARM pipeline failed. For the SPHARM and the cortical thickness methods, the subjects for whom the corresponding pipeline failed could not be classified with the SVM and were therefore excluded from the training set. As for the testing set, since those subjects were neither misclassified nor correctly classified, they were considered as 50% misclassified. This approach was chosen because a failure of the pipeline is a weakness of the methods.

On the training set, cross-validation (CV) was used to estimate the optimal values of hyperparameters. In general, there is only one hyperparameter which is the cost parameter *C* of the linear C-SVM. In *Voxel-STAND*, there is a second parameter which is the threshold *t* of feature selection. In *Voxel-COMPARE*, a second parameter is the size σ of the Gaussian kernel and the third parameter is the number *n* of selected features. In *Hippo-Volume*, there is no hyperparameter. The optimal parameter values were determined using a grid-search and leave-one-out cross validation (LOOCV) on the training set. The grid search was performed over the ranges $C = 10^{-5}$, $10^{-4.5}$, ..., $10^{2.5}$, 10^3 , t = 0.06, 0.08, ..., 0.98, $\sigma = 100$, 200, ..., 1000 and n = 1, 2, ..., 150 (except for *Voxel-COMPARE* were $C = 10^0$, 10^1 , $10^{1.5}$, 10^2 , $10^{2.5}$).

For each approach, the optimized set of hyperparameters was then used to train the classifier using the training group; the performance of the resulting classifier was then evaluated on the testing set. In this way, we achieved unbiased estimates of the performances of each method.

For each method, we computed the number of true positives TP (i.e. the number of diseased individuals which were correctly identified by the classifier), the number of true negatives TN (i.e. the number of healthy individuals which were correctly identified by the classifier), the number of false positives FP (i.e. the number of healthy individuals which were not correctly identified by the classifier), the number of false negatives FN (i.e. the number of diseased individuals which were not correctly identified by the classifier). We then computed the sensitivity defined as TP/(TP + FN), the specificity defined as TN/(TN + FP), the positive predictive value defined as PPV = TP/(TP + FP), the negative predictive value defined as NPV = TN/(TN + FN). Finally it should be noted that the number of subjects in each group is not the same. The classification accuracy does not enable to compare the performances between the different classification experiments. Thus we considered both the specificity and the sensitivity instead.

To assess whether each method performs significantly better than a random classifier, we used McNemar's chi square tests. Significance level was set at 0.05. We also used McNemar's chi square tests to assess differences between DARTEL and SPM5 registrations and between classification results obtained using only GM and using all three maps. The McNemar test investigates the difference between proportions in paired observations. We used it to assess the difference between proportions of correctly classified subjects, i.e. accuracy. The corresponding contingency table is presented in Table 3.

Results

Classification results

The results of the classification experiments are summarized in Tables 4, 5 and 6 respectively for CN vs AD, CN vs MCIc and CN vs MCIc. The classification results of CN vs AD and CN vs MCIc are also represented in Fig. 1. In each table, the different methods are referred to either by their abbreviation or by their number defined in Table 2.

CN vs AD

The classification results for CN vs AD are summarized in Table 4 and in Fig. 1. All methods performed significantly better than chance (p<0.05). The four Voxel methods (Voxel-Direct, Voxel-STAND, Voxel-Atlas, Voxel-COMPARE) classified AD from CN with very high specificity (over 89%) and high sensitivity: 75% for Voxel-STAND and over 81% for the other three methods. Methods based on the cortical thickness led to similar results with at least 90% specificity and 69%, 74% and 79% respectively for Thickness-ROI, Thickness-Direct and Thickness-Atlas. The hippocampus-based strategies were as sensitive but less specific: between 63% for Hippo-Volume and 84% for Hippo-Shape.

CN vs MCIc

Classification results for CN vs MCIc are summarized in Table 5 and in Fig. 1. Most methods were substantially less sensitive than for AD vs CN classification. All methods except *Voxel-COMPARE* and the *Hippo* methods obtained significantly better results than a random classifier (p<0.05). There was no substantial difference between the results obtained with *Voxel-Direct, Voxel-Atlas* and *Voxel-STAND*. All those methods reached a high specificity (over 85%) but a sensitivity ranging between 51% (*Voxel-COMPARE*) and 73% (*Voxel-STAND*). The methods based on cortical thickness behave as well as the previous ones. *Hippo-Volume* was slightly less specific but as sensitive as for the AD vs CN classification.

MCInc vs MCIc

The classification results for MCInc vs MCIc are summarized in Table 5. Only four methods managed to predict conversion slightly more accurately than a random classifier but none of them got significantly better results (p>0.05). *Thickness-Direct* reached 32% sensitivity and 91% specificity. *Voxel-STAND* reached 57% sensitivity and 78% specificity, *Voxel-COMPARE* reached 62% sensitivity and 67% specificity. *Hippo-Volume* distinguished MCIc from MCInc with 62% sensitivity and 69% specificity.

Table 3

Contingency table for the McNemar test. a: number of subjects correctly classified by both classifiers; b: number of subjects correctly classified by classifier 1 but misclassified by classifier 2; c: number of subjects misclassified by classifier 1 but correctly classified by classifier 2; and d: number of subjects misclassified by both classifiers.

	Classifier 2: correctly classified	Classifier 2: misclassified
Classifier 1: correctly classified	a	b
Classifier 1: misclassified	C	d
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Table 4

Classification results CN vs AD.

		CN vs AD				
Method #	Method's name	SEN	SPE	PPV	NPV	McNemar test
1.1.1 a	Voxel-Direct-D-gm	81%	95%	93%	86%	p<0.0001
1.1.1 b	Voxel-Direct-D-all	68%	98%	96%	78%	p<0.0001
1.1.2 a	Voxel-Direct-S-gm	72%	89%	84%	79%	p<0.0001
1.1.2 b	Voxel-Direct-S-all	65%	88%	81%	75%	p<0.0001
1.2.1 a	Voxel-Direct_VOI-D-gm	71%	95%	92%	79%	p<0.0001
1.2.1 b	Voxel-Direct_VOI-D-all	65%	95%	92%	76%	p<0.0001
1.2.2 a	Voxel-Direct_VOI-S-gm	65%	91%	86%	76%	p<0.0001
1.2.2 b	Voxel-Direct_VOI-S-all	59%	81%	73%	70%	p = 0.0012
1.3.1 a	Voxel-STAND-D-gm	69%	90%	85%	78%	p<0.0001
1.3.1 b	Voxel-STAND-D-all	71%	91%	87%	79%	p<0.0001
1.3.2 a	Voxel-STAND-S-gm	75%	91%	88%	81%	p<0.0001
1.3.2 b	Voxel-STAND-S-all	75%	86%	82%	80%	p<0.0001
1.3.3 a	Voxel-STAND-Sc-gm	72%	91%	88%	80%	p<0.0001
1.3.3 b	Voxel-STAND-Sc-all	71%	91%	87%	79%	p<0.0001
1.4.1 a	Voxel-Atlas-D-gm	78%	93%	90%	83%	p<0.0001
1.4.1 b	Voxel-Atlas-D-all	81%	90%	87%	85%	p<0.0001
1.4.2 a	Voxel-Atlas-S-gm	75%	93%	89%	82%	p<0.0001
1.4.2 b	Voxel-Atlas-S-all	74%	93%	89%	81%	p<0.0001
1.5.1 a	Voxel-COMPARE-D-gm	82%	89%	86%	86%	p<0.0001
1.5.1 b	Voxel-COMPARE-D-all	69%	81%	76%	76%	p<0.0001
1.5.2 a	Voxel-COMPARE-S-gm	66%	86%	80%	75%	p<0.0001
1.5.2 b	Voxel-COMPARE-S-all	72%	91%	88%	80%	p<0.0001
2.1	Thickness-Direct	74%	90%	86%	80%	p<0.0001
2.2	Thickness-Atlas	79%	90%	87%	84%	p<0.0001
2.3	Thickness-ROI	69%	94%	90%	78%	p<0.0001
3.1.1	Hippo-Volume-F	63%	80%	73%	72%	p = 0.0007
3.1.2	Hippo-Volume-S	71%	77%	72%	76%	p = 0.0006
3.2	Hippo-Shape	69%	84%	78%	76%	p<0.0001

SEN: sensitivity; SPE: specificity; PPV: positive predictive value; and NPV: negative predictive value.

Influence of the preprocessing

To evaluate the impact of the registration step, we tested both the registration using SPM5 unified segmentation and the registration

Table 5	
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Classification results CN vs MCIc.

		CN vs MCIc				
Method #	Method's name	SEN	SPE	PPV	NPV	McNemar test
1.1.1 a	Voxel-Direct-D-gm	57%	96%	88%	83%	p = 0.00052
1.1.1 b	Voxel-Direct-D-all	49%	91%	72%	80%	p = 0.046
1.1.2 a	Voxel-Direct-S-gm	32%	96%	80%	76%	p=0.039
1.1.2 b	Voxel-Direct-S-all	41%	94%	75%	78%	p = 0.044
1.2.1 a	Voxel-Direct_VOI-D-gm	54%	95%	83%	82%	p = 0.0022
1.2.1 b	Voxel-Direct_VOI-D-all	41%	96%	83%	78%	p = 0.0095
1.2.2 a	Voxel-Direct_VOI-S-gm	32%	88%	55%	74%	p=0.83
1.2.2 b	Voxel-Direct_VOI-S-all	22%	99%	89%	73%	p = 0.046
1.3.1 a	Voxel-STAND-D-gm	73%	85%	69%	87%	p = 0.025
1.3.1 b	Voxel-STAND-D-all	65%	93%	80%	85%	p = 0.0019
1.3.2 a	Voxel-STAND-S-gm	59%	86%	67%	82%	p = 0.082
1.3.2 b	Voxel-STAND-S-all	49%	93%	75%	80%	p = 0.025
1.3.3 a	Voxel-STAND-Sc-gm	62%	85%	66%	83%	p = 0.091
1.3.3 b	Voxel-STAND-Sc-all	57%	90%	72%	82%	p = 0.026
1.4.1 a	Voxel-Atlas-D-gm	65%	80%	60%	83%	p=0.27
1.4.1 b	Voxel-Atlas-D-all	54%	91%	74%	81%	p = 0.021
1.4.2 a	Voxel-Atlas-S-gm	68%	95%	86%	87%	p = 0.00020
1.4.2 b	Voxel-Atlas-S-all	59%	94%	81%	84%	p = 0.0021
1.5.1 a	Voxel-COMPARE-D-gm	49%	81%	55%	78%	p = 0.73
1.5.1 b	Voxel-COMPARE-D-all	51%	85%	61%	79%	p=0.28
1.5.2 a	Voxel-COMPARE-S-gm	49%	78%	50%	77%	p = 0.87
1.5.2 b	Voxel-COMPARE-S-all	59%	78%	55%	81%	p = 0.64
2.1	Thickness-Direct	54%	96%	87%	82%	p = 0.00084
2.2	Thickness-Atlas	57%	93%	78%	82%	p = 0.0071
2.3	Thickness-ROI	65%	94%	83%	85%	p = 0.00083
3.1.1	Hippo-Volume-F	73%	74%	56%	86%	p = 0.47
3.1.2	Hippo-Volume-S	70%	73%	54%	84%	p = 0.67
3.2	Hippo-Shape	57%	88%	68%	82%	p = 0.072

SEN: sensitivity; SPE: specificity; PPV: positive predictive value; and NPV: negative predictive value.

Tab	le 6	
- 1		

Classification results MCInc vs MCIc.

		MCInc vs MCIc				
Method #	Method's name	SEN	SPE	PPV	NPV	McNemar test
1.1.1 a	Voxel-Direct-D-gm	0%	100%	-	64%	p = 1.0
1.1.1 b	Voxel-Direct-D-all	0%	100%	-	64%	p = 1.0
1.1.2 a	Voxel-Direct-S-gm	0%	100%	-	64%	p = 1.0
1.1.2 b	Voxel-Direct-S-all	0%	100%	-	64%	p = 1.0
1.2.1 a	Voxel-Direct_VOI-D-gm	43%	70%	44%	69%	p = 0.62
1.2.1 b	Voxel-Direct_VOI-D-all	0%	100%	-	64%	p = 1.0
1.2.2 a	Voxel-Direct_VOI-S-gm	0%	100%	-	64%	p = 1.0
1.2.2 b	Voxel-Direct_VOI-S-all	0%	100%	-	64%	p = 1.0
1.3.1 a	Voxel-STAND-D-gm	57%	78%	58%	76%	p = 0.40
1.3.1 b	Voxel-STAND-D-all	0%	100%	-	64%	p = 1.0
1.3.2 a	Voxel-STAND-S-gm	22%	91%	57%	68%	p = 0.79
1.3.2 b	Voxel-STAND-S-all	51%	79%	58%	75%	p = 0.49
1.3.3 a	Voxel-STAND-Sc-gm	35%	70%	39%	66%	p = 0.30
1.3.3 b	Voxel-STAND-Sc-all	41%	72%	44%	69%	p = 0.61
1.4.1 a	Voxel-Atlas-D-gm	0%	100%		64%	p = 1.0
1.4.1 b	Voxel-Atlas-D-all	0%	100%	-	64%	p = 1.0
1.4.2 a	Voxel-Atlas-S-gm	0%	100%		64%	p = 1.0
1.4.2 b	Voxel-Atlas-S-all	0%	100%	-	64%	p = 1.0
1.5.1 a	Voxel-COMPARE-D-gm	62%	67%	51%	76%	p = 1.0
1.5.1 b	Voxel-COMPARE-D-all	54%	78%	57%	75%	p = 0.50
1.5.2 a	Voxel-COMPARE-S-gm	32%	82%	50%	69%	p = 0.84
1.5.2 b	Voxel-COMPARE-S-all	51%	72%	50%	73%	p = 0.87
2.1	Thickness-Direct	32%	91%	67%	71%	p = 0.24
2.2	Thickness-Atlas	27%	85%	50%	68%	p = 0.82
2.3	Thickness-ROI	24%	82%	43%	66%	p = 0.66
3.1.1	Hippo-Volume-F	70%	61%	50%	79%	p=0.89
3.1.2	Hippo-Volume-S	62%	69%	52%	77%	p=0.88
3.2	Hippo-Shape	0%	100%	-	64%	p = 1.0

SEN: sensitivity; SPE: specificity; PPV: positive predictive value; and NPV: negative predictive value.

DARTEL as described in the previous section. The influence of the registration step on the classification results is illustrated on Figs. 2 and 3. The performances obtained for the MCInc vs MCIc experiment were too low to be used to evaluate the impact of the registration step. Therefore we did not take them into account for this comparison. The use of the diffeomorphic registration algorithm DARTEL significantly improved the results of six out of 20 classification experiments (p<0.05). On the other hand, it led to significantly worse results in two cases. According to the results in Tables 4, 5, and 6, the use of customized tissue probability maps for the registration with SPM5 unified segmentation did not improve the results of *Voxel-STAND*.

We also compared the classification obtained with only the GM maps to those with GM, WM and CSF maps. Results are presented on Figs. 2 and 3. The use of all three maps led to significantly worse results (p<0.05) for two out of 20 classification experiments (*Voxel-Direct_VOI-S* and *Voxel-COMPARE-D*). It never led to significantly better results.

Complementariness of the methods

The different approaches tested tackle the classification problem with various angles and could thus be complementary. In order to quantify their similarity, we used the Jaccard similarity coefficient (Jaccard, 1901; Shattuck et al., 2001). In this case, the Jaccard index of two methods is the number of subjects correctly classified by both methods divided by the number of subjects correctly classified by at least one of the two methods. Results are presented on Figs. S1 and S2. All methods are in at least substantial agreement (Jaccard over 0.6) and most of them are in strong agreement. The most different results were obtained with the methods relying on the hippocampus.

We tested the combination of three approaches, one of each strategy: *Voxel-Direct-D-gm, Thickness-Atlas* and *Hippo-Volume-S.* A convenient approach to combine different SVM-based methods is to consider that the resulting classifier is a SVM which kernel is a linear

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Fig. 1. Classification results for the different methods.

convex combination of the kernels of each method. The problem of learning both the coefficients of the best convex linear combination of kernels and the optimal margin hyperplane (OMH) is known as the multiple kernel learning (MKL) problem (Lanckriet et al., 2004; Bach et al., 2004; Sonnenburg et al., 2006). We used the SimpleMKL toolbox (Rakotomamonjy et al., 2008). All four possible combinations have been tested. The kernels are normalized with the trace of the Gram matrix of the training set. Note that for *Hippo-Volume-S*, the Parzen window classifier is replaced by a linear SVM.

None of these four combinations improved the accuracy in the CN vs AD experiment. Only the combination of *Hippo-Volume-S* and *Thickness-Atlas* improved only slightly the accuracy for the CN vs MCIc and the MCInc vs MCIc experiments. It distinguished MCIc from CN with 76% sensitivity and 85% specificity. The optimal coefficients of the linear combination were 0.057 and 0.943 for the kernels of *Hippo-Volume-S* and *Thickness-Atlas*, respectively. This combination classified MCIc and MCInc with 43% sensitivity and 83% specificity. The

optimal coefficients of the linear combination were 0.030 and 0.970 respectively.

Influence of age and gender on classification results

We investigated whether the age of the subjects influences the classification results. We thus computed the average age of true positives, false positives, true negatives and false negatives. Overall, we found that the false positives were often older than the true negatives, meaning that the oldest controls were more often misclassified. Specifically, this was the case for 25 methods over 28 for CN *vs* AD and 24/28 for CN *vs* MCIc. Conversely, false negatives were often younger than the true positives, meaning that the youngest patients were more often misclassified. Specifically, this was the case for 26 methods over 28 for CN *vs* AD and 28/28 for CN *vs* MCIc. The number of misclassified subjects was too small to test for statistical significance of these differences. However, the fact that this difference was present for the vast majority of method suggests that it

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Fig. 2. Impact of the preprocessing on the accuracy for CN *vs* AD. The sum of the sensitivity and specificity is considered. The front tip of an arrow indicates the results obtained with DARTEL whereas the back tip indicates the results obtained with SPM5 unified segmentation. The color of the arrow indicates the features used. Grey arrows correspond to the use of GM probability maps only whereas white arrows correspond to the use of GM, WM and CSF probability maps. The p-values obtained with the McNemar's chi square test assessed the difference between the results obtained with DARTEL and SPM5.

may not be due to chance. We also investigated the influence of gender but did not find any difference.

Computation time

The computations were carried out with a processor running at 3.6 GHz with 2 GB of RAM. Table 7 presents, for each method, the order of magnitude of the computation time (i.e. minutes, hours, days, and weeks). For each method, we report the computation time of its three main phases: the feature computation step (segmentation and registration), the building of the classifier (including the grid search for the optimization of the hyperparameters and the learning of the classifier), and the classification of a new subject.

The order of magnitude of the computation time for the tissue segmentation and the registration step per subject is respectively about ten minutes and an hour with SPM5 and DARTEL. The cortical thickness computation and the registration of a single subject with FreeSurfer take roughly a day. The segmentation of the hippocampi of a subject lasts a few minutes and the shape analysis process with the SPHARM decomposition about one hour. The tuning of parameters and learning phase took from a few minutes to several weeks for the *Voxel-STAND* and *Voxel-COMPARE* methods. Once the hyperparameters are set and the learning is done, it takes at most minutes to classify a new subject.

Optimal margin hyperplanes

The classification function obtained with a linear SVM is the sign of the inner product of the features with w, a vector orthogonal to the

optimal margin hyperplane (OMH) (Vapnik, 1995; Shawe-Taylor and Cristianini, 2000, 2004; Schölkopf and Smola, 2001). Therefore if the ith component w_i of the vector w is small, the ith feature will have a small influence on the classification. Conversely, if w_i is large, the ith feature will play an important role in the classifier. When the input features are the voxels of the image, each component of w also corresponds to a voxel. One can thus represent the values of w in the image space. Similarly, for the *Thickness* methods, the values of w can be represented on the cortical surface. The values of the optimal margin hyperplanes for the different methods are presented on Figs. from 4 to 7. This allows a qualitative comparison of the features used in the classifier. Our aim was not to perform a statistical analysis of differences between groups — for example using permutation tests on the coefficients (Mourao-Miranda et al., 2005).

Figs. 4 and 5 show the OMH for CN vs AD and CN vs MCIc respectively for the Voxel methods. Overall, the spatial patterns corresponding to CN vs AD and CN vs MCIc are similar. For Voxel-Direct-D-gm, the main regions were the medial temporal lobe (hippocampus, amygdala and the parahippocampal gyrus), the inferior and middle temporal gyri, the posterior cingulate gyrus and the posterior middle frontal gyrus. To a lesser extent, the OMH also included the inferior parietal lobule, the supramarginal gyrus, fusiform gyrus, the middle cingulate gyrus and in the thalamus. When all three tissue maps were used, the CSF maps mirrored the GM map (the enlargement of the ventricle mirroring GM reduction). This was also the case for part of the WM map, in particular in the hippocampal region. When using SPM5 unified segmentation instead of DARTEL, voxels were much more scattered and not grouped into anatomical regions except in the medial temporal lobe. For the AAL

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Fig. 3. Impact of the preprocessing on the accuracy for CN vs MCIc. The sum of the sensitivity and specificity is considered. The front tip of an arrow indicates the results obtained with DARTEL whereas the back tip indicates the results obtained with SPM5 unified segmentation. The color of the arrow indicates the features used. Grey arrows correspond to the used of GM probability maps only whereas white arrows correspond to the use of GM, WM and CSF probability maps. The p-values obtained with the McNemar's chi square test assessed the difference between the results obtained with DARTEL and SPM5.

atlas, regions included the hippocampus, the amygdala, the parahippocampal gyrus, the cingulum, the middle and inferior temporal gyri and the superior and inferior frontal gyri. The regions were very similar for the surface Atlas as shown on Fig. 6. Regions corresponding to *Thickness-Direct* (Fig. 7) were more restricted: the entorhinal cortex, the parahippocampal gyrus and to a lesser extent the lateral temporal lobe, the inferior parietal lobule and some prefrontal areas.

Optimal parameters of the classifiers

For each approach, the optimal values of the hyperparameters are summarized in Table S1. One should note that the *Hippo-Volume* method has no hyperparameter.

Discussion

In this paper, we compared different methods for the classification of patients with AD and MCI based on anatomical T1-weighted MRI. To evaluate and compare the performances of each method, three classification experiments were performed: CN vs AD, CN vs MCIc and CN vs MCInc. The set of participants was randomly split up into two groups of the same size: a training set and a testing set. For each approach, the optimal parameter values had been determined using a grid-search and LOOCV on the training set. Those values were then used to train the classifier using the training group; the performance of the resulting classifier was then evaluated on the testing set. In this way, we obtained unbiased estimates of the performances of each method.

Classification methods discriminate AD from normal aging

All the classification methods that we tested in this paper achieved accuracies significantly better than chance for the discrimination of patients with AD from normal aging. All methods except *Voxel-COMPARE* and *Hippo* methods performed significantly better than chance for the discrimination of patients with prodromal AD (MCIc) from normal aging. For AD vs CN, most methods achieved high sensitivity and specificity. However, at the prodromal stage, their sensitivity was substantially lower.

The classification results we obtained for AD vs CN with Atlas and COMPARE methods are lower than those reported in the respective papers: 94% accuracy for the COMPARE method in (Fan et al., 2008a) and 92% sensitivity and 97% specificity for the Atlas in Magnin et al. (2009). These differences can be explained by several factors. First, in the original papers, the hyperparameters were optimized on the testing set. This may lead to overfitting the testing set and thus to overestimate the sensitivity and specificity. On the contrary, in our evaluation, the learning step as well as the optimization of the hyperparameters had been carried out on a training set and the evaluation of the performance on a completely separated testing set. Thus our evaluation was unbiased. Another explanation may stem from differences between studied populations (sample size, stage of the disease). In particular, the ADNI population includes a large number of subjects with vascular lesions, which was not the case in Magnin et al. (2009). Finally, the image preprocessing step may also have an impact on the classification results. Davatzikos et al. (2008b) and Fan et al. (2008b) used the RAVENS maps (Goldszal et al., 1998),

Table 7

Order of magnitude of the computation time (i.e. minutes, hours, days, and weeks) for each method for its three main phases: feature computation step (segmentation and registration), building of the classifier (including the grid search for the optimization of the hyperparameters and the learning of the classifier), and classification of a new subject. The computations have been carried out with a processor running at 3.6 GHz with 2 GB of RAM.

Method #	Method's name	Segmentation registration	Grid search learning	Testing
1.1.1 a	Voxel-Direct-D-gm	Hour(s) per subject	Minute(s)	Minute(s)
1.1.1 b	Voxel-Direct-D-all	Hour(s) per subject	Minute(s)	Minute(s)
1.1.2 a	Voxel-Direct-S-gm	10 min per subject	Minute(s)	Minute(s)
1.1.2 b	Voxel-Direct-S-all	10 min per subject	Minute(s)	Minute(s)
1.2.1 a	Voxel-Direct_VOI-D-gm	Hour(s) per subject	Minute(s)	Minute(s)
1.2.1 b	Voxel-Direct_VOI-D-all	Hour(s) per subject	Minute(s)	Minute(s)
1.2.2 a	Voxel-Direct_VOI-S-gm	10 min per subject	Minute(s)	Minute(s)
1.2.2 b	Voxel-Direct_VOI-S-all	10 min per subject	Minute(s)	Minute(s)
1.3.1 a	Voxel-STAND-D-gm	Hour(s) per subject	Day(s)	Hour(s)
1.3.1 b	Voxel-STAND-D-all	Hour(s) per subject	Week(s)	Hour(s)
1.3.2 a	Voxel-STAND-S-gm	10 min per subject	Day(s)	Hour(s)
1.3.2 b	Voxel-STAND-S-all	10 min per subject	Week(s)	Hour(s)
1.3.3 a	Voxel-STAND-Sc-gm	20 min per subject	Day(s)	Hour(s)
1.3.3 b	Voxel-STAND-Sc-all	20 min per subject	Week(s)	Hour(s)
1.4.1 a	Voxel-Atlas-D-gm	Hour(s) per subject	Minute(s)	Minute(s)
1.4.1 b	Voxel-Atlas-D-all	Hour(s) per subject	Minute(s)	Minute(s)
1.4.2 a	Voxel-Atlas-S-gm	10 min per subject	Minute(s)	Minute(s)
1.4.2 b	Voxel-Atlas-S-all	10 min per subject	Minute(s)	Minute(s)
1.5.1 a	Voxel-COMPARE-D-gm	Hour(s) per subject	Week(s)	Hour(s)
1.5.1 b	Voxel-COMPARE-D-all	Hour(s) per subject	Week(s)	Hour(s)
1.5.2 a	Voxel-COMPARE-S-gm	10 min per subject	Week(s)	Hour(s)
1.5.2 b	Voxel-COMPARE-S-all	10 min per subject	Week(s)	Hour(s)
2.1	Thickness-Direct	Day(s) per subject	Minute(s)	Minute(s)
2.2	Thickness-Atlas	Day(s) per subject	Minute(s)	Minute(s)
2.3	Thickness-ROI	Day(s) per subject	Minute(s)	Seconds
3.1.1	Hippo-Volume-F	Day(s) per subject	Minute(s)	Seconds
3.1.2	Hippo-Volume-S	10 min per subject	Minute(s)	Seconds
3.2	Hippo-Shape	Hour(s) per subject	Minute(s)	Seconds

thus the registration and the segmentation step was different and might lead to different classification results. However, the aim of the present paper was to compare different classification strategies and it was thus necessary to use the same preprocessing for all methods. Since most of them relied on SPM, we chose to use this preprocessing for all methods. It is possible that using other registration approaches such as HAMMER would increase the classification performance but this is beyond the scope of this paper.

For the *Voxel-STAND* and *Voxel-Direct* methods, our results were similar to those reported in the original papers by Vemuri et al. (2008) and Klöppel et al. (2008). This can probably be explained by the fact that Vemuri et al.'s (2008) evaluation procedure is also based on independent testing group and that Klöppel et al. (2008) did not mention any optimization of the hyperparameters. As for the *Thickness-ROI*, the results (69% sensitivity and 94% specificity) were lower than those obtained by Desikan et al. (2009) (100% specificity and sensitivity). A possible explanation is that in their study the classifier was trained on a different population (patients with CDR = 0.5) selected from a different database (the OASIS database).

The results obtained with Hippo-Volume were similar to those that we previously reported for the ADNI database (Chupin et al., 2009b). The sensitivities and specificities were however lower than those found in our previous study on a different population (Colliot et al., 2008) (84% sensitivity and specificity for CN vs AD). This can be explained by several factors (Chupin et al., 2009b). First ADNI is a multi-site database whereas the data in the previous study came from a single scanner. Moreover the population included a large number of subjects with vascular lesions. The slight difference between the results obtained in Chupin et al. (2009b) and the present results mostly comes from the difference in the accuracy estimation: two separate groups instead of a LOOCV procedure. As for the Hippo-Shape method the results were substantially lower than our results reported in Gerardin et al. (2009) (86% for CN vs AD). This may result from the relatively small number of subjects used in our previous study. Besides, the estimation was carried out with a LOOCV. Moreover, this can also be due to that fact that all subjects were considered without



Fig. 4. Optimal margin hyperplane in the CN vs AD experiments for *Voxel-Direct-D-gm* (a), *Voxel-Direct-D-all* (b–d), *Voxel-Direct-S-gm* (e), *Voxel-STAND-D-gm* (f) and *Voxel-Atlas-D-gm* (g). The figure displays the normalized vector orthogonal to the hyperplane superimposed on the tissue average probability maps. The coronal slices are equivalent to y = 9 mm in the MNI-space. For visualization purposes, only coefficients w_i greater than 0.15 in absolute value are displayed. For regions in warm colors, tissue atrophy increases the likelihood of classification into AD or MCIc. For regions in cool colors, it is the opposite. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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Fig. 5. Optimal margin hyperplane in the CN vs MCIc experiments for Voxel-Direct-D-gm (a), Voxel-Direct-D-all (b-d), Voxel-Direct-S-gm (e), Voxel-STAND-D-gm (f) and Voxel-Atlas-D-gm (g) (please refer to Fig. 4 for a complete description of the figure). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

taking into consideration the quality control (Chupin et al., 2009b) of the hippocampus segmentation.

To our knowledge, the classification CN vs MCIc has only been addressed by Desikan et al. (2009). Davatzikos et al. (2008a) and Fan et al. (2008a,b) have performed the classification CN vs MCI with no distinction between converters and non-converters. The MCI group did not include only prodromal AD, hence the classification experiment cannot be compared to CN vs MCIc. Desikan et al. (2009) classified CN and MCI who converted within two years after baseline with 91% accuracy. This is substantially higher than the results obtained in our

paper with the same method *Thickness-ROI* (65% sensitivity and 94% specificity).

Prediction of conversion in MCI patients

No method was able to predict conversion better than chance. The three most accurate methods were: *Voxel-STAND* (57% sensitivity and 78% specificity), *Voxel-COMPARE* (62% sensitivity and 67% specificity) and *Hippo-Volume* (62% sensitivity and 69% specificity). These three methods restricted their search to a portion of the brain. In *Voxel-STAND*



Fig. 6. Optimal margin hyperplane for Thickness-Atlas. Upper rows: CN vs AD experiment. Lower rows: CN vs MClc experiment.

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Fig. 7. Optimal margin hyperplane for Thickness-Direct. Upper rows: CN vs AD experiment. Lower rows: CN vs MClc experiment.

and *Voxel-COMPARE*, this was done using feature selection: the selected regions are mainly in the medial temporal structures. In *Hippo-Volume*, this was done by considering only the hippocampus.

Even for these three methods, the performances remained particularly low. The main reason is certainly that MCI non converters are a very heterogeneous group: some patients would convert shortly after the end of the follow-up and are thus in fact prodromal AD patients while others would remain stable for a long period of time. We thus advocate that classification methods should be focused on the detection of prodromal AD (i.e. MCI converters) which is a much better defined entity.

To our knowledge, the classification MCInc vs MCIc has only been addressed by Misra et al. (2009) and Querbes et al. (2009). Misra et al. (2009) considered the conversion within 12 months and Querbes et al. (2009) within 24 months. They obtained substantially higher accuracy: respectively 81.5% and 76% accuracy. Misra et al. (2009) used the COMPARE (Fan et al., 2007) classification methods. The differences may result from the same reasons as explained in the previous paragraph: the use of separate training and testing sets and differing preprocessing steps. Querbes et al. (2009) used a feature selection step, which may explain the slightly higher accuracy.

Whole brain or hippocampus?

For CN vs AD, methods using the whole brain (or the whole cortex) reached substantially higher specificity (over 90%) than those based on the hippocampus (from 63% to 84%). For the detection of prodromal AD, hippocampal-based approaches remained competitive with whole-brain methods. It thus seems that considering the whole brain is advantageous mostly at the most advanced stages. Indeed, at these more advanced stages, the atrophy is much more widespread. Moreover, it should be noted that many subjects included in the ADNI have vascular lesions which may be, at least partially, captured by whole brain methods. For intermediate stages, an alternative would be to consider a set of selected regions instead of the whole brain or the hippocampus alone. For example, *Thickness-ROI* performs at least as well as whole brain approaches for the detection of prodromal AD. Even though they achieve lower accuracies, hippocampal-based methods may still be of interest to the clinician because they provide

a direct and easily interpretable index to the clinician (the hippocampal volume) while the whole-brain approaches base their classification on a complex combination of different regions.

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All methods presented substantial agreement (Jaccard index over 0.6). The most different results were obtained between hippocampal and whole brain methods. However, combining them through multiple kernel learning did not improve the classification results.

The registration step: is a fully deformable method advantageous?

The use of DARTEL significantly improved the classification results in six cases, while it led to lower results in only two cases. This is in line with other studies which reported that DARTEL led to higher overlap values (Klein et al., 2009; Yassa and Stark, 2009) and higher sensitivity for voxel-based morphometry (Bergouignan et al., 2009). In particular, the use of a fully deformable method was advantageous for the medial temporal lobe as shown in (Yassa and Stark, 2009; Bergouignan et al., 2009). Since the hippocampus is highly affected in AD, we expected that using a method which registers the hippocampus better, would result in higher classification accuracy.

Does adding WM and CSF maps increase the performance of the classifiers?

In their original description, some of the tested methods used the three tissue (GM, WM and CSF) maps (e.g. Vemuri et al., 2008, Fan et al., 2007, Magnin et al., 2009) while others used only the GM maps (e.g. Klöppel et al., 2008). In this paper, we systematically tested whether the compared methods performed better with the three maps or with only the GM maps. It should be noted that this does not aim at assessing the diagnostic value of WM or CSF in general but only to test if including all tissue maps is more effective for these particular classification approaches under study. On the whole, adding the WM and the CSF probability maps did not improve the classification performances. Adding WM and CSF maps increases the dimensionality of the feature space which can make the classifier unstable and lead to overfitting the data. This problem is well-known in machine learning as the curse of dimensionality. Besides, elder subjects are likely to have WM structural abnormalities caused by leucoaraiosis or other diseases. Therefore adding WM tissues may add noise in the features. Even if WM structural

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abnormalities alter (Levy-Cooperman et al., 2008) the tissue segmentation step, GM probability maps are more robust features than WM tissues probability maps.

Adding the WM and the CSF in the features may improve the results in two instances. The first one is when the method encloses a feature selection step. Methods including feature selection steps are more able to keep only the added value and avoid considering the noise but, overall, the improvement is not substantial. Adding WM and CSF may also improve the results of methods grouping the voxels into ROIs via wrapping a labeled atlas. It may make up for the parcellation error due to the registration step but, again, the improvement is not substantial.

Is it worth performing feature selection?

The main objectives of the feature selection step are to keep only informative features and to reduce the dimensionality of the feature space. In our evaluation, two methods included a feature selection step: *Voxel-STAND* and *Voxel-COMPARE*. Overall, these methods did not perform substantially better than simpler ones. In particular, their results might be more sensitive to the training set. Indeed, feature selection can be regarded as a learning step. In such a case, the feature selection step increases the class of all possible classification functions, which could lead to overfitting the data. A more robust way to decrease the dimensionality of the features way would be to use more prior knowledge of the disease.

Besides features selection can be time consuming as it adds new hyperparameters and thus makes the grid search less tractable. Compared to *Voxel-Direct* and *Voxel-Atlas*, *Voxel-STAND* and *Voxel-COMPARE* are time consuming (up to weeks), mostly because of the number of hyperparameters to be tuned.

Nevertheless, feature selection proved useful in two specific cases. First, these methods proved less sensitive when increasing the dimensionality of the feature space by adding WM and CSF maps. They also tended to be more accurate for the MCIc vs MCInc experiment, where only a few brain regions are informative.

Does age influence the classification accuracy?

Overall, we found that the oldest controls and the youngest patients were more often misclassified. This may results from different causes. Normal aging is associated with atrophy of the grey and white matter and increase of the CSF (Good et al., 2001; Salat et al., 2004). Moreover, aging is also associated with alterations in tissue intensity and contrast, which can disrupt the segmentation step and thus artificially increase the measured atrophy (Salat et al., 2009). Besides, elderly subjects are more likely to have structural abnormalities of the white matter, which can also impede the tissue segmentation step (Levy-Cooperman et al., 2008) and increase the measured atrophy. In addition, elderly subjects have a propensity to suffer from mixed dementia (Zekry et al., 2002).

Optimal margin hyperplanes

In a linear SVM, the OMH can be easily represented. The OMH provides information about the regions of the brain which was used by the classifier. It should be noted that this only provides qualitative information on the hyperplanes, and that no statistical analysis of the OMH coefficients was performed.

With Voxel-Direct-D, Voxel-Atlas and Thickness-Atlas, the regions in which atrophy increased the likelihood of being classified as AD or MCIc were largely consistent with the pattern of atrophy demonstrated in previous morphometric studies. These regions included the medial temporal lobe, the inferior and middle temporal gyri (Chételat and Baron, 2003; Good et al., 2002; Busatto et al., 2003; Rusinek et al., 2004; Tapiola et al., 2005; Laakso et al., 1998) and the posterior

middle frontal gyrus (Whitwell et al., 2007), the fusiform gyrus, the thalamus (Karas et al., 2003, 2004; Chételat et al., 2005). As for the cortical methods, the main regions in the medial temporal, middle and inferior lateral temporal, inferior parietal, and posterior cingulated cortices and with a lesser extent parietal, frontal, and lateral occipital cortices, which is consistent with the previous group studies based on cortical thickness (Thompson et al., 2004; Lerch et al., 2005, 2008; McDonald et al., 2009).

In conclusion, we compared different automatic classification methods to assist in the early diagnosis of Alzheimer's disease using the ADNI database. Most of them classify AD and CN with high accuracy. However, at the prodromal stage, their sensitivity was substantially lower. Combinations with other markers and/or more sophisticated prior knowledge seem necessary to be able to detect prodromal AD with high accuracy.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.06.013.

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Résumé

L'hippocampe est une structure de substance grise du lobe temporal du cerveau qui joue un rôle fondamental dans les processus de mémoire ainsi que dans de nombreuses pathologies (maladie d'Alzheimer, épilepsie, dépression...). Le développement de modèles morphométriques est essentiel pour étudier l'anatomie fonctionnelle de cette structure et les altérations associées à différentes pathologies. L'objectif de cette thèse est de développer et de valider des méthodes de morphométrie de l'hippocampe dans deux contextes distincts : l'étude de la forme externe de l'hippocampe à partir d'IRM conventionnelles (1.5T ou 3T) à résolution millimétrique, l'étude de sa structure interne à partir d'IRM 7T à très haute résolution spatiale. Ces deux contextes correspondent aux deux parties principales de la thèse. Dans une première partie, nous proposons une méthode pour la classification automatique de patients à partir de descripteurs morphométriques. Cette méthode repose sur une décomposition en harmoniques sphériques qui est combinée à un classifieur de type support vector machine (SVM). La méthode est évaluée dans le contexte de la classification automatique de patients avec une maladie d'Alzheimer (MA), de patients mild cognitive impairment (MCI) et de sujets sains âgés. Elle est également comparée à d'autres approches et une validation plus exhaustive est proposée dans une population de 509 sujets issus de la base ADNI. Nous présentons enfin une autre application de la morphométrie pour l'étude des altérations structurelles associées au syndrome de Gilles de la Tourette. La seconde partie de la thèse est consacrée à la morphométrie de la structure interne de l'hippocampe à partir d'IRM à 7 Tesla. En effet, la structure interne de l'hippocampe est riche et complexe mais inaccessible à l'IRM conventionnelle. Nous proposons tout d'abord un atlas de la structure interne de l'hippocampe à partir de données postmortem acquises à 9.4T. Ensuite, nous proposons de modéliser la corne d'Ammon et le subiculum sous la forme d'un squelette et d'une mesure locale d'épaisseur. Pour ce faire, nous introduisons une méthode variationnelle originale utilisant des espaces de Hilbert à noyaux reproduisants. La méthode est ensuite validée sur l'atlas postmortem et évaluée sur des données in vivo de sujets sains et de patients avec épilepsie acquises à 7T.
Abstract

The hippocampus is a gray matter structure in the temporal lobe that plays a key role in memory processes and in many diseases (Alzheimer's disease, epilepsy, depression ...). The development of morphometric models is essential for the study of the functional anatomy and structure alterations associated with different pathologies. The objective of this thesis is to develop and validate methods for morphometry of the hippocampus in two contexts: the study of the external shape of the hippocampus from conventional MRI (1.5T or 3T) with millimeter resolution, and the study of its internal structure from 7T MRI with high spatial resolution. These two settings correspond to the two main parts of the thesis. In the first part, we propose a method for the automatic classification of patients from shape descriptors. This method is based on a spherical harmonic decomposition which is combined with a support vector machine classifier (SVM). The method is evaluated in the context of automatic classification of patients with Alzheimer's disease (AD) patients, mild cognitive impairment (MCI) patients and healthy elderly subjects. It is also compared to other approaches and a more comprehensive validation is available in a population of 509 subjects from the ADNI database. Finally, we present another application of morphometry to study structural alterations associated with the syndrome of Gilles de la Tourette. The second part of the thesis is devoted to the morphometry of the internal structure of the hippocampus from MRI at 7 Tesla. Indeed, the internal structure of the hippocampus is rich and complex but inaccessible to conventional MRI. We first propose an atlas of the internal structure of the hippocampus from postmortem data acquired at 9.4T. Then, we propose to model the Ammon's horn and the subiculum as a skeleton and a local measure thickness. To do this, we introduce a variational method using original Hilbert spaces reproducing kernels. The method is validated on the postmortem atlas and evaluated on in vivo data from healthy subjects and patients with epilepsy acquired at 7T.