Neurobiological Significance of Automatic Segmentation: Application to the Early Diagnosis of Alzheimer's Disease

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Abstract. Alzheimer's disease is a progressive neurodegenerative disease that affects particularly memory function. Specifically, the neural system responsible for encoding and retrieval of the memory for facts and events (declarative memory) is dependent on anatomical structures located in the medial part of the temporal lobe (MTL). Clinical lesions as well as experimental evidence point that the hippocampal formation (hippocampus plus entorhinal cortex) and the adjacent cortex, both main components of the MTL, are the regions critical for normal declarative memory function. Neuroimage studies as ours, have taken advantage of the feasibility of manual segmentation of the gray matter volume, which correlates with memory impairment and clinical deterioration of Alzheimer's disease patients. We wanted to explore the advantages of automatic segmentation tools, and present results based on one 3T MRI in a young subject. The automatic segmentation allowed a better discrimination between extracerebral structures and the surface of the brain, as well as an improvement both in terms of speed and reliability in the demarcation of different MTL structures, all of which play a key role in declarative memory processing. Based largely on our own nonhuman primate data on brain and hippocampal connections, we defined automatically the angular bundle in the MTL as the fibers containing the perforant path (interconnection and dialogue between the entorhinal cortex and its hippocampal termination. The speed and accuracy of the technique needs further development, but it seems to be promising enough for early detection of memory deficits associated to Alzheimer's disease.

1 Introduction

Alzheimer's disease (AD) belongs to a group of neurodegenerative diseases, which affect a large percentage of the population. As the longevity of the general

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population increases, so does the incidence of the disease. This incapacitating disease is a tremendous burden on the patient, families and society in general, that see a staggering increase in economic expenditure, both at the pharmacological and social costs levels of caregivers and institutions.

One of the early symptoms of the disease is a profound memory loss that leaves AD patients unable to find their way home, to recognize their closest relatives, and finally, totally dependent on the care provided by family or institutional caregivers. The perspective of treatment for those patients is bleak, as there is no treatment available that can stop the progress of the disease. Certain chemical substances (namely acetylcholine), that decrease as a consequence of the neuronal death of a certain group of neurons present at the base of the brain, offer some delay in the progression of the symptoms, but the effect is relatively small (the more so as the stage of the disease is higher), being more effective when symptoms are diagnosed at an early stage. Still, the economic cost of the treatment imposes a big economic burden on patients and their families. Those early stages are often classified as "Mild Cognitive Impairment" or MCI, usually affecting memory alone [12].

Notwithstanding, a great deal has been advanced through intensive research throughout the world on the biochemical and molecular basis of the disease, that inspired new treatments, still in need of testing in controlled clinical trials. In essence, two are the hallmarks of the disease: one is the deposition of a substance called amyloid that seems to be toxic to nearby neurons; the second one is the load of abnormally phosphorilated neurofilaments. Neurofilaments are normal cell scaffolding that keeps the shape of neurons and is a normal constituent, which turn abnormal in the disease and ultimately kill the neurons with all their processes, both dendrites (which receive neural information) and axons (which transmit the neural information to other neurons, some close to the parent neuron, some distant, the latter forming bundles of fibers that constitute the white matter of the brain).

The neuronal death that as the acumulation of amyloid substance in the form of neuritic plaques, and abnormal neurofilaments in the form of neurofibrillary tangles, prevent the normal function of the nervous system, what causes a loss of function of different neural systems. Among those neural systems is the memory system, which comprises several types of memory (mainly non-declarative memory and declarative memory). Since 1957 is known to clinicians and neuropsychologists that the hippocampal system, located at the medial part of the temporal lobe, the lobe adjacent to the temple and running backwards to join the occipital lobe, is the brain structure that enables every person to form permanent memories for biographical events and facts of the external world. This region is made up of different components the hippocampal formation [7] made up of the hippocampus proper, and the adjacent subicular and entorhinal cortices. The latter is especially relevant in the transfer of supramodal sensory modalities to the hippocampus through the perforant path, already described by Ramón y Cajal more than one hundred years ago and continued presently [8]. The hippocampus elaborates the information and through several relays, projects back

to the entorhinal cortex, which returns it to different regions of the cortex for permanent storage. Different lines of research in experimental animals, mainly in nonhuman primates and rodents [11], as well as in patients that presented lesions in the medial temporal lobe (MTL) have shown that the hippocampus is not the repository of memories, but rather its function is instrumental in the formation and consolidation of declarative memory.

Two recent reports underscore the importance of this pathway in the detection of AD at its early stages. Kalus reported a preliminary study [10] in which the technique of diffusion tensor imaging (DTI) is used to evaluate the perforant path in a series of 10 control subjects, 10 MCI and 10 AD patients. They found a correlation between anisotropy values of the perforant path and the separation between MCI and controls, in contrast to both hippocampal and entorhinal cortex volumes that did not show significant differences. Another study, in a larger clinical sample (50 controls and 40 amnestic MCI patients) was reported by Stoub [12]. They explored specifically declarative memory (dependent on the integrity of the hippocampal formation and surrounding cortex), and concluded that the volume of the hippocampus and the volume of the white matter of the perforant path zone were significant predictors of memory function. Several other reports in the literature show the damage in the neurons origin of the perforant path ad the termination zones at different levels of the hippocampus mainly in Alzheimer's disease, but present as well in other pathological conditions [4,13,14].

For this reason, we aimed at evaluating the application of automatic segmentation of the gray and white matter to detect the course and volume of the bundle of fibers that interconnect the entorhinal cortex and the hippocampus, that is, the perforant path, as a means to detect subtle changes in the size, course and termination of this fundamental brain pathway that, surprisingly, is still relatively little explored with neuroradiological techniques, despite it was recognized since more than 25 years ago to be the region most susceptible to show pathological changes in AD [5,3].

2 Methods

We have employed a series of sections of a 3T MRI on which an automatic segmentation by means of SPM detected the gray matter, the cerebrospinal fluid space (CSF) and the white matter. In the latter, we focused on the white matter subjacent to the entorhinal cortex.

SPM is a software package for analysis of neuroimages that provides a unified segmentation procedure [1] that cyclicaly combines voxel classification, bias correction and spatial normalization of the image. SPM uses two methods for voxel classification: a) the standard SPM method uses knowledge of the tissue spatial distribution represented by tissue probability maps; b) the method implemented in VBM5 (an extension of SPM) uses knowledge of the neigbourhood of the voxel, modeled by Hidden Markov Random Fields [2]. This second method provided a finer segmentation. Prior to the segmentation was necessary to register the image with respect to the MRI template used by SPM (*T1.nii*). To this end,

Table 1. Configuration parameters for MRI normalization and segmentation

Phase	Parameter	Value
Register / Normalise	Affine regularization	ICBM space template
	Wrapping	No wrap
Segment	Use tissue priors	No priors (experimental)
	HMRF weighting	medium HMRF (0.3)
	Clean up any partitions	Light clean

we used the SPM function "Normalise". The parameters used for normalization and segmentation of the image are shown in Table 1.

3 Results

We have followed the general principles on which we previously demonstrated the feasibility and advantage of the identification and adaptation of neuroanatomical criteria reported in [6] followed by a validation study [9] in which the volume

Table 2. Anatomical structures found at different slices of the brain's coronal view

Section / Distance in mm	Structural MRI		Segmented white matter	
	Right hemisphere	Left hemisphere	Right hemisphere	Left hemisphere
248 / 0.5	*Limen insulae*			
247 / 1			*Limen insulae*	
245 / 2		*Limen insulae*		
243 / 3				*Limen insulae*
234 / 7.5	Amigdala	Amigdala	Amigdala	Amigdala
214 / 17.5	*Diverticulum unci*	*Diverticulum unci*	*Diverticulum unci*. Angular bundle	*Diverticulum unci*. Angular bundle
197 / 21	*Gyrus intralimbicus*		*Gyrus intralimbicus*	
194 / 22.5		*Gyrus intralimbicus*		*Gyrus intralimbicus*
186 / 26.5	Lateral geniculate nucleus	Lateral geniculate nucleus	Lateral geniculate nucleus	Lateral geniculate nucleus
163 / 38	Fornix		Fornix	
154 / 42.5		Fornix		Fornix
149 / 45.5	End of hippocampus		End of hippocampus	
137 / 51.5		End of hippocampus		End of hippocampus

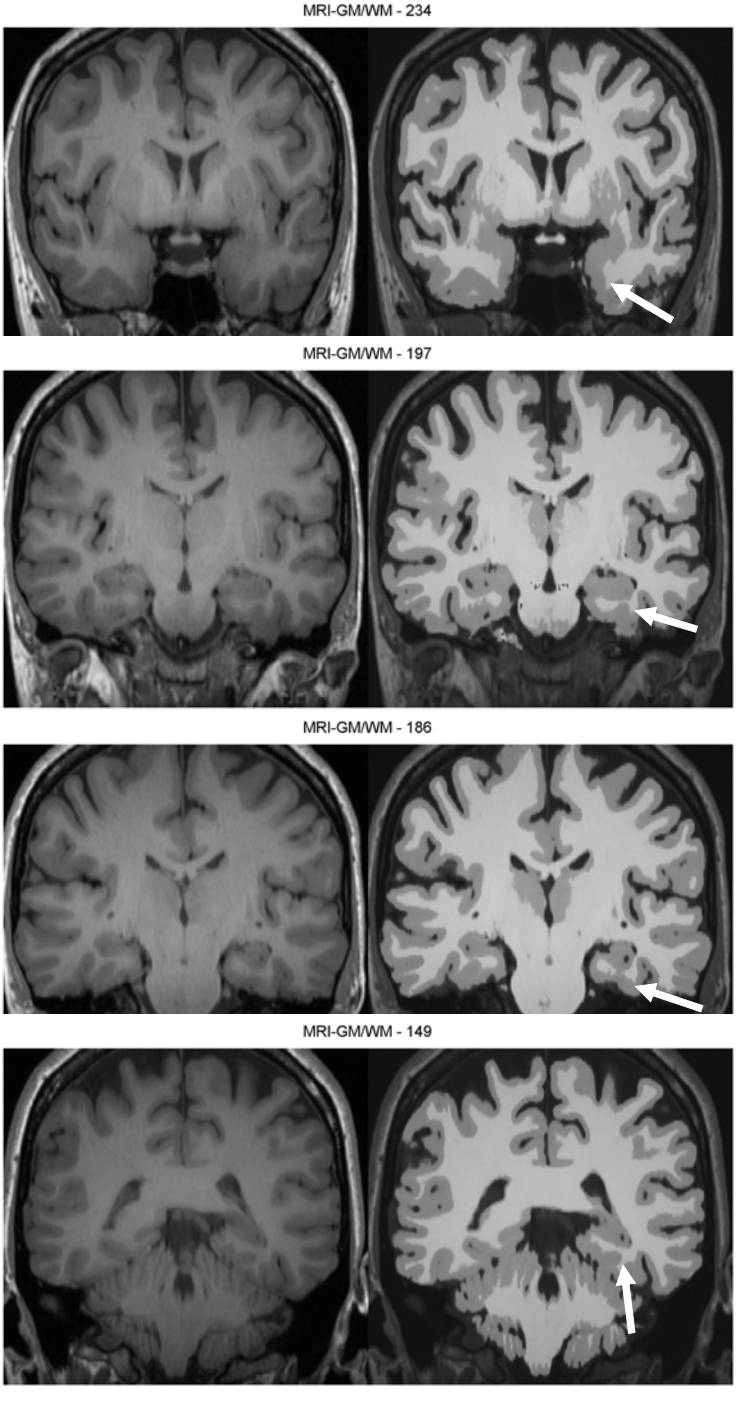

Fig. 1. Angular bundle (white arrow) throughout the longitudinal extent of the MTL

of the entorhinal cortex is found to correlate with the severity of dementia in Alzheimer's disease.

Several points have been selected in our study to highlight the identification of the perforant path, taking into consideration that the perforant path is not recognizable in itself, but rather, and derived from analysis performed on the brain of nonhuman primates, it travels along the angular bundle which contains other kind of fibers, which is easily recognizable on MRI images, and presents a constant location, no matter how decreased its size might be.

The automatic segmentation of the white matter discriminates some confounding structures, such as brain blood arteries, venous sinuses as the petrous sinus and emissary veins to the entorhinal cortex and nearby cortical areas; finally, it avoids duramater structures such as the tentorium cerebelli. In consequence, it "cleans" the image, and this fact, along the structural T1 weighted images, helps in the recognition of the angular bundle. It is worth considering too the anterior choroidal artery, which runs along the choroidal (hippocampal) fissure, that at the same time, may obscure the medial border of the entorhinal and subicular cortices. Also, the automatic segmentation of the white matter defines much better the ventral limit of the amygdala, important to define the upper limit of the angular bundle at its more rostral portion, rendering the image of the angular bundle easier and faster for delimitation.

The segmentation of the white matter offers additional advantages in the delimitation of the medial part of the uncus, a particularly convoluted portion of the hippocampus, that is an essential landmark for the precise delimitation of the caudal end of the entorhinal cortex , approximately 2 mm behind the gyrus intralimbicus, [6]. Likewise, the caudal portion of the hippocampus, also very convoluted, and sectioned in an oblique plane stands much more clearly. Portions of the white matter in the medial temporal lobe contain the axons of the neurons that interconnect the entorhinal cortex and the hippocampus, an essential pathway for memory processing. This pathway is known as the perforant path, which runs in a larger bundle (the angular bundle) that in addition to the perforant path, contains other cortical association fibers, mostly between frontal and temporal lobes as well as association fibers intrinsic to the temporal lobe.

A summary of our results is presented in table 2, referred to a single case analysis, in which some of the images of the angular bundle along its rostrocaudal axis are shown. Figure 1 depicts a T1 image at 3T and the corresponding automatically segmented image that renders visible the angular bundle (white arrow) throughout the longitudinal extent of the MTL.

4 Discusion

Technological advances in medical imaging technology offer a wealth of new possibilities to detect, diagnose and plan a therapeutic plan for a large segment of the population. However, the optimal situation would be a multidisciplinary approach to medical problems by the interaction of different areas of expertise in a single team. We combined some of these fields, and the preliminary

results are here presented. By the adaptation of informatic tools, we were able to demonstrate the feasibility of automatically segmenting an important bundle of nervous fibers, the perforant path embedded in the angular bundle, which is instrumental in the normal process of memory for facts and events.

It is worth noting that this memory processing in the medial temporal lobe is highly impaired in Alzheimer's disease, partially through damage to the angular bundle. From the identification along the longitudinal axis of the medial temporal lobe, it ensures the possibility of volumetric measurement almost automatically. Moreover, at every instant the evaluator can compare the non-segmented MRI images and the segmented ones to adjust to neuroanatomical criteria that still await elaboration.

An additional advantage can be envisioned, namely the much easier feasibility of longitudinal studies in persons at certain age to follow the volume variation of the angular bundle.

Nowadays, while there is little doubt that the volumetric measurement of the anatomical structures of the MTL, including the amygdala show volumetric changes that indicate the neuronal loss, typical of AD pathology, it is still a debate issue whether or not this approach is useful in the detection of early stages of AD, namely the MCI. Moreover, many of those studies are well controlled clinical trials in which a great deal of time is necessary to manually trace the MRI limits of the anatomical structures important to declarative memory. Unfortunately, this time and effort expenditure is not possible in many clinical circumstances, and therefore leaves the potential AD patients without the possibility of an early diagnosis, although neuropsychological and clinical follow-up determine the division of these two broad categories, MCI and AD. It is particularly worrisome that precisely it is at the earliest stages where the pharmacological treatment can be most effective in the maintenance of the intellectual capabilities and independence in daily live activities. For this reason, we deemed important to devise a protocol that might be simple and able to be applied to a broad segment of the elderly population based on the estimation of the anatomical identification of the perforant path amid other fiber bundles that all together constitute the angular bundle, easily recognizable along the rostrocaudal extent of the MTL. A preliminary analysis on the feasibility of this approach, based on automatic transformation tools is presented here.

Our hypothesis and future direction of our work is that a refinement of this approach, after appropriate clinical testing, might be able to provide the necessary sensibility to detect more subtle changes that may ultimately lead to an early diagnosis, before clinical symptoms appear, of an evolution towards a clinically flourished Alzheimer disease.

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