Automatic Morphological Analysis of Medial Temporal Lobe

Andrea Chincarini[1], Mirko Corosu[1], Gianluca Gemme[*,1], Piero Calvini[1,2], Roberta Monge[1,2], Maria Antonietta Penco[1,2], Luca Rei[1,2], Sandro Squarcia[1,2], Patrizia Boccacci[3] and Guido Rodriguez[4]

[1]*National Institute of Nuclear Physics (INFN), Genoa Division, Genoa, Italy*

[2]*Department of Physics, University of Genoa, Genoa, Italy*

[3]*Department of Informatics, University of Genoa, Genoa, Italy*

[4]*Clinical Neurophysiology, Department of Neuroscience, Ophthalmology and Genetics, University of Genoa, Genoa, Italy*

Abstract: Research in Alzheimer's disease (AD) has seen a tremendous growth of candidate biomarkers in the last decade. The role of such established or putative biomarkers is to allow an accurate diagnosis of AD, to infer about its prognosis, to monitor disease progression and evaluate changes induced by disease-modifying drugs. An ideal biomarker should detect a specific pathophysiological feature of AD, not present in the healthy condition, in other primary dementias, or in confounding conditions. Besides being reliable, a biomarker should be detectable by means of procedures which must be relatively non-invasive, simple to perform, widely available and not too expensive. At present, no candidate meets these requirements representing the high standards aimed at by researchers. Among others, various morphological brain measures performed by means of magnetic resonance imaging (MRI), ranging from the total brain volume to some restricted regions such as the hippocampal volume, have been proposed. Nowadays the efforts are directed toward finding an automated, unsupervised method of evaluating atrophy in some specific brain region, such as the medial temporal lobe (MTL). In this work we provide an extensive review of the state of the art on the automatic and semi-automatic image processing techniques for the early assessment of patients at risk of developing AD. Our main focus is the relevance of the morphological analysis of MTL, and in particular of the hippocampal formation, in making the diagnosis of AD and in distinguishing it from other dementias.

Keywords: Alzheimer disease, medial temporal lobe, hippocampus, MRI.

INTRODUCTION

During the last decade, interest in magnetic resonance imaging (MRI) of neurodegenerative diseases has been rapidly rising. Much of this increased interest is due to the growth in the incidence and prevalence of these diseases, caused by population aging in the industrialized countries (especially the United States, Europe, and Japan) [1]. In addition, the imaging techniques have become more refined, especially due to the development of computer-assisted image processing tools with quantification of the volumes of brain structures. Finally, improved knowledge concerning the pathophysiological mechanisms of neurodegenerative diseases, especially Alzheimer's disease (AD), has led to the development of putative treatments which are entering clinical trials [2]. The scientific community have recognized that imaging techniques are "supportive features" in the diagnosis of probable AD [3], and can be used to monitor the effects of treatments slowing disease progression. All of these factors have led to an outburst of interest in the imaging of neurodegenerative diseases, culminating in the funding of the Alzheimer's Disease Neuroimaging Initiative (ADNI). This very large multi-site study uses MRI, positron emission tomography (PET), and biomarkers, together with clinician measures, to monitor disease progression (further information at http: //www.ADNI-info.org).

Despite the lack of a disease-modifying treatment at present, the discovery of sensitive and specific markers of early AD would represent a major breakthrough as it would allow – once this treatment is available – to slow (and hopefully even to stop) the degenerative process before dementia develops. Furthermore, current symptomatic treatments may be more efficient when administered in the early stages of AD [4]. However, early diagnosis remains difficult to achieve, and currently the clinical diagnosis of AD can be made relatively late during the disease progression. The difficulties lie mostly in the similarities between the cognitive impairment due to normal aging processes and the early symptoms of AD. The diagnosis of clinically probable AD can currently be made in living subjects only once the stage of dementia has been reached. It is based on a number of criteria as defined by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) [3, 5], but can be confirmed only by postmortem histopathology. While the clinical signs of AD are well established, the early symptomatic and predementia stage remains to be better defined [6].

*Address correspondence to this author at the Istituto Nazionale di Fisica Nucleare, Sezione di Genova, via Dodecaneso, 33, Genova I-16146, Italy; Tel: +39 010 3536227; Fax: +39 010 313358;
E-mail: gianluca.gemme@ge.infn.it

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In recent years, the early clinical signs of AD have been extensively investigated, leading to the concept of amnestic mild cognitive impairment (aMCI), an intermediate cognitive state between normal aging and dementia [7-11]. aMCI patients experience memory loss to a greater extent than expected for age, and they progress to a diagnosis of AD at a faster rate than controls [7, 8]. Conversion rates typically range from 1 to 3 years, with an average rate of 20 months [12]. Nevertheless aMCI remains a clinically and pathologically heterogeneous state in need of more extensive definition and classification [13]. Emerging disease-modifying treatments should be used in the aMCI subset with prodromal AD and not in a wider population with uncertain pathology [14].

Such findings imply a need of improved tools for MRI-based volumetric analyses that are suitable for routine clinical use. Furthermore, although many efforts are underway to develop treatments that could prevent AD or slow its progression, these efforts are also partially hindered by the lack of practical yet sensitive *in vivo* biomarkers that may help demonstrate the disease-modifying effects of potential treatments and to identify those patients most likely to benefit from an aggressive protocol. Both of these needs might be better addressed by efficient methods for the quantitative measurement of atrophy in the living brain.

THE ROLE OF NEUROIMAGING

A challenge for modern neuroimaging is to help in the diagnosis of early AD, particularly in aMCI patients. Three-dimensional (3D) MRI with high spatial resolution allows the visualization of subtle anatomic changes and thus can help detect brain atrophy in the initial stages of the disease [15]. Therefore sensitive neuroimaging measures have been investigated to quantify structural changes in the brain in early AD, which are automated enough to permit large-scale studies of the disease and of the factors that affect it. To track the disease process, several MRI-based measures have been proposed. Many studies have searched for optimal volumetric measures (e.g., of the hippocampus or entorhinal cortex) to differentiate normal aging from AD, and from aMCI [16]. The goal of research in this area is therefore to develop highly specific and sensitive tools capable of identifying as early as possible among at-risk subjects those who will most likely progress to AD.

The segmentation of sub-cortical structures in brain MRI is of paramount importance for many clinical and neuroscientific investigations. In many studies on the evolution of the neurodegenerative process, sub-cortical structures must typically be segmented in large populations of patients and healthy controls, in order to quantify disease progression over time, to detect factors influencing structural changes, and to measure response to treatment. To date, these studies have particularly focused on assessing atrophy of medial temporal lobe (MTL) structures [6, 17-20]. A common biological marker of disease progression is the morphological change in the hippocampus, because it is known to occur early in the course of the disease on a spatial scale large enough to be detectable in structural MRI [18, 21] or by mapping the spatial distribution of atrophy in 3D [14, 22-24]. By means of MRI at millimeter resolution, subtle hippocampal shape changes can be resolved [16].

Many researchers have thus assessed hippocampal atrophy in AD by using manual segmentation in MRI [25-35]. These studies have demonstrated that manual MR volumetry of the hippocampus can help distinguish patients with AD from elderly controls with a high degree of accuracy (80% - 90%). However, the manual segmentation of the hippocampus requires a high degree of anatomic training and is observer dependent and time consuming. The tracing by hand of both hippocampi represents a tedious task requiring a time between 30 mins and 2 hours; it quickly causes fatigue and the accuracy of the result may be affected. On the other hand visual evaluation of atrophy in 3D MRI, although more suited for clinical practice, is prone to subjectivity [36].

Automatic Methods

Methods to assess hippocampal atrophy have been largely based on volumetric measurements [28, 21, 18], on mapping the spatial distribution of atrophy in 3D scans [14, 22-24, 37], or on visual rating scales [38]. Volumetric measurements typically rely on manual outlining of MTL structures on (serial) MR images, which is time-consuming and prone to interrater and intrarater variability. Thus, large-scale studies of AD-related hippocampal atrophy are often impractical [39]. A number of studies were published where the visual rating scale was used in memory clinic population [40-47]. However, the scale, although simple to use and suitable for a clinical application, was not designed to detect atrophy progression on serial imaging; its quantized nature makes it insensitive to subtle changes over time [44].

In order to accelerate and spread epidemiological studies and clinical trials, some automated systems have been proposed for hippocampal segmentation.

In [48], the authors explore whether the application of local registration and calculation of the hippocampal boundary shift integral (HBSI) can reduce random variation in comparison with manual measures. Hippocampi were outlined on the baseline and registered on the follow-up MRIs of 32 clinically diagnosed AD patients and 47 matched controls (37–86 years) with a wide range of scanning intervals (175–1173 days). The scans were globally registered using 9 degrees of freedom, and subsequently locally registered using 6 degrees of freedom, and HBSI values were then calculated automatically. The use of HBSI significantly reduced the mean rate ($P < 0.01$) and variation in controls ($P < 0.001$) and increased group separation between AD cases and controls. When comparing HBSI atrophy rates with manually derived atrophy rates at 90% sensitivity, specificities were 98% and 81%, respectively. From logistic regression models, a 1% increase in HBSI atrophy rates was associated with an 11-fold increase in the odds of a diagnosis of AD. For manually derived atrophy rates, the equivalent odds ratio was 3. The authors conclude that HBSI-derived atrophy rates reduce operator time and error, and are at least as effective as the manual equivalent as a diagnostic marker and represent a potential marker of progression in longitudinal studies and trials.

Crum *et al.* describe the application of voxel-level 3D registration onto serial MRIs [49]. Their fluid registration determines a deformation field modeling brain change, which is consistent with a model describing the flow of a

viscous fluid. The objective was to validate the measurement of hippocampal volumetric change in AD by fluid registration against current methodologies. First, the convergence, repeatability, linearity, and accuracy of the method were investigated and compared with expert manual segmentation. A simple model of hippocampal atrophy was used to compare simulated volumetric changes against those obtained by fluid registration. Finally the serial segmentation was compared with the current gold standard technique – expert human labeling with a volume repeatability of approximately 4% – in 27 subjects (15 normal controls, 12 clinically diagnosed with AD). The scan-rescan volumetric consistency of serial segmentation by fluid-registration was shown to be superior to human serial segmentors (approximately 2%). The mean absolute volume difference between fluid and manual segmentation was 0.7%. For these reasons this fluid registration approach has a potential importance for tracking longitudinal structural changes in the brain, particularly in the context of clinical trials where a large number of subjects may have multiple MRI scans.

However, both methods described above require the manual segmentation of the baseline hippocampal region.

Fischl *et al*. present a technique for automatically assigning a neuroanatomical label to each voxel in an MRI volume based on the probabilistic information automatically estimated from a manually labeled training set [50]. In contrast with other segmentation procedures that only label a small number of tissue classes, this method assigns one of 37 labels to each voxel, including left and right caudate, putamen, pallidum, thalamus, lateral ventricles, hippocampus, and amygdala. The classification technique employs a registration procedure that is robust to anatomical variability, including the ventricular enlargement typically associated with neurological diseases and aging. The technique is shown to be comparable in accuracy to manual labeling, and of sufficient sensitivity to robustly detect changes in the volume of noncortical structures that presage the onset of probable AD. The method helped identify significant group differences in terms of hippocampal volume, but the authors did not investigate the classification of individual participants.

In [51] the authors verified the precision and reproducibility of deformation-based hippocampal segmentations in the MRIs of five patients with mesial temporal sclerosis. The overall percentage overlap between automated segmentations was 92.8% (SD, 3.5%), between manual segmentations was 73.1% (SD, 9.5%), and between automated and manual segmentations was 74.8% (SD, 10.3%). Thus, such deformation-based hippocampal segmentations are shown to provide a precise method of hippocampal volume measurement in this population.

Powell *et al*. propose several automated segmentation methods based on a multidimensional registration and give a direct comparison between their methods and various template, probability, artificial neural network and support vector machine based automated segmentation methods [52]. Three metrics for each segmentation method are reported in the delineation of sub-cortical and cerebellar brain regions. Results show that the machine learning methods outperform the template and probability-based methods. Utilization of these automated segmentation methods may be as reliable as manual raters and require no rater intervention.

Wang *et al*. describe how in the framework of a large-deformation diffeomorphic metric mapping (LDDMM) the diffeomorphic matching of images is modeled as the change with time of a flow of an associated smooth velocity vector field v controlling the evolution [53]. The initial momentum parameterizes the whole geodesic and encodes the shape and form of the target image. Thus, methods such as principal component analysis (PCA) of the initial momentum allow to study anatomical shape and form in target images with no restriction to the small-deformation assumption in the analysis of linear displacements. The authors apply this approach to a study of AD. The left hippocampus in the AD group shows significant shape abnormality. A similar pattern of abnormality is shared by the right hippocampus. Furthermore, PCA of the initial momentum leads to the correct classification of 12 out of 18 very mild AD subjects (Clinical Dementia Rating Scale, CDR=0.5) and 22 out of 26 control subjects.

Yushkevich *et al*. developed an open source application called ITK-SNAP, which is intended to make level set segmentation easily accessible to a wide range of users, including those with little or no mathematical expertise [54]. Their work describes the methods and software engineering philosophy behind this new tool and provides the results of validation experiments performed in the context of a neuroimaging study of ongoing child autism. The validation establishes SNAP intrarater and interrater reliability and overlap error statistics for the caudate nucleus and finds that SNAP is a highly reliable and efficient alternative to manual tracing. Analogous results for lateral ventricle segmentation are provided.

However none of these and other methods [51, 55-59], is yet widely used [16] due to high computational burden [60], unsatisfactory results [61], or poor generalization capability [50].

Moreover, while several automated hippocampal segmentation methods have been proposed, most of them rely either on the manual identification of several hippocampal landmarks on each scan [23, 51, 62, 63], or on algorithms based on the intensities and spatial anatomical relationship of different brain structures to guide hippocampal outlining [50, 64]. Webb *et al*. [65] devised an automated method to detect hippocampal atrophy in patients with temporal lobe epilepsy based on the analysis of the image intensity differences between patients and controls within a volume of interest centered on the hippocampus. Rusinek *et al*. [66] used the boundary shift integral analysis applied to a volume of interest centered on the hippocampus to calculate the rate of MTL atrophy.

Few of these methods have been applied to patients with AD and/or MCI and rarely did researchers report the accuracy of their techniques in the differentiation among MCI, AD and controls. Carmichael *et al*. [39] have assessed the performance of automated atlas-based segmentation by applying to AD and MCI patients several freely available registration methods: Automated Image Registration [University of California at Los Angeles, Los Angeles, CA], Statistical Parametric Mapping [Wellcome Department of

Imaging Neuroscience], Functional MRI Linear Image Registration Tool [University of Oxford, Oxford, England], and a fully deformable approach. They came to the conclusion that these approaches are less precise when applied to AD patients than controls but this should be tempered by the fact that these techniques were not specifically designed for this task. Csernansky *et al*. [67] used the high-dimensional brain mapping approach, on the basis of fluid registration with a template, to obtain hippocampal volumes and hippocampal shape differences between patients with very mild AD and controls. By using a classification on the basis of volume and shape features, they achieved a sensitivity of 83% and a specificity of 78%. By using a similar high-dimensional brain mapping approach, Hsu *et al*. [62] compared automated and manual segmentations in AD and cognitively impaired patients. They reported good correlations between manual and automated measurements of the hippocampal volume. However, they did not investigate the accuracy of this technique for the classification of individual patients. Colliot *et al*. [68] evaluated the accuracy of automated hippocampal volumetry to help distinguish between patients with AD, patients with MCI, and elderly controls. Individual classification on the basis of hippocampal volume resulted in 84% correct classification (sensitivity, 84%; specificity, 84%) between AD patients and controls and 73% correct classification (sensitivity, 75%; specificity, 70%) between MCI patients and controls. Ridha *et al*. [44] compared an automated intensity-based measure of MTL atrophy (ATLAS) with volumetric and visually based methods. Their measure differentiates patients with AD from controls at cross-sectional and longitudinal levels. At baseline, for a specificity of 85%, the sensitivity of hippocampal volume measurement and visual rating scale [38] were similar (84% *vs* 86%), whereas the sensitivity of the ATLAS measure was lower at 73%.

In a recent work [69] a novel approach, based on the measure of a new statistical indicator, the Δ-box score, able to separate the AD, aMCI and controls cohorts, was introduced. In this work the authors describe the development of a simple, quick, and operator independent method to extract two subimages (one for each side of the brain) from a MR image, containing both the hippocampus and the perihippocampal region. A novel statistical indicator, which measures MTL atrophy, is computed on the intensities in the automatically extracted subimages. This novel indicator was applied to a sample of 150 mild AD patients (MMSE score 23.2 ± 4.1), 247 aMCI, and 135 healthy controls. Significant differences of MTL atrophy were detected both in AD and in aMCI cohorts (AD *vs* controls 0.28 ± 0.03 *vs* 0.34 ± 0.03, $P < 0.001$; aMCI *vs* controls 0.31 ± 0.03 *vs* 0.34 ± 0.03, $P < 0.001$). MTL atrophy in the subgroup of 25 aMCI converters was similar to the one evaluated in the AD group, and was significantly different from the one of the controls (0.27 ± 0.03 *vs* 0.34 ± 0.03, $P < 0.001$).

Individual classification on the basis of the Δ-box score was also analyzed by using the receiver operating characteristic (ROC) curves, which indicate the relationship between sensitivity and 1-specificity for each intergroup discrimination. The area under the curve was 0.863 for AD patients *vs* controls, 0.746 for aMCI patients *vs* controls, and 0.880 for aMCI converters *vs* controls. With specificity set at 85%, the sensitivity was 74% for AD *vs* controls, 45% for aMCI *vs* controls, and 83% for aMCI converters *vs* controls.

This method is able to capture differences between subgroups of interest with different stages of cognitive impairment, with comparable discriminating capability between aMCI converters and controls, and between AD patients and controls. However, this and other results should be considered with caution owing to the relatively small number of converters. Anyway, this is in agreement with several studies regarding the manual segmentation of hippocampus, which have reported that baseline hippocampal volume is an indicator of future progression to AD [21, 70-73]. This is also in agreement with studies based on visual rating, which clearly found MTL atrophy in patients who subsequently converted to AD [74-76].

Compared to other methods of hippocampal or MTL atrophy measurement, this method, which does not directly tackle the objective of hippocampus segmentation, is fully automated, allowing the analysis of large sets of data, and requires relatively moderate image postprocessing and prerequisites for automation. Therefore, it could be a good candidate for being more widely used than other automatic methods.

Local Analysis to Assess the Spatial Distribution of Atrophy

While the detection of hippocampal volume changes has been the focus of most image processing studies because of its relatively straightforward interpretation, the popularity of more sophisticated approaches based on shape analysis is increasing as they promise a more accurate localization of changes in hippocampal surfaces. Shape analysis and/or classification methods using both local and global information may give complementary information and improve classification reliability.

In [77], the authors propose a method for the mapping of hippocampal (HC) surfaces to establish correspondences between points on HC surfaces and enable localized HC shape analysis. A novel geometric feature, the intrinsic shape context, is defined to capture the global characteristics of the HC shapes. Based on this intrinsic feature, an automatic algorithm is developed to detect a set of landmark curves that are stable across population. The direct map between a source and target HC surface is then solved as the minimizer of a harmonic energy function defined on the source surface with landmark constraints. For numerical solutions, the authors compute the map with the approach of solving partial differential equations on implicit surfaces. The direct mapping method has the advantage of being automatic, and it is invariant to the position of HC shapes. The direct mapping method is applied to study temporal changes of HC asymmetry in AD using HC surfaces from 12 AD patients and 14 normal controls. The results show that the AD group has a different trend in temporal changes of HC asymmetry than the group of normal controls, and demonstrate the flexibility of the direct mapping method by applying it to construct spherical maps of HC surfaces. Spherical harmonics analysis is then applied and it confirms the results on temporal changes of HC asymmetry in AD.

Evidence from neuropathologic studies supports the specific role of neuronal loss in the CA1 region and subiculum [24, 78]. Reliable detection *in vivo* of hippocampal changes that are more specific to AD, particularly at the pre-clinical or early clinical stage, has important clinical ramifications and is an area of active research [79, 80]. Scher *et al*. [81] analyze hippocampal size and regional shape differences as a means of distinguishing the AD-affected hippocampus from hippocampal changes associated with normal aging. They use structural imaging techniques to model hippocampal size and regional shape differences between elderly men with incident AD and a non-demented comparison group of elderly men. Participants were diagnosed with incident AD (n=24: age=82.5±4.6) or were non-demented (n=102: age=83.0±5.9). One reader, blinded to dementia diagnosis, manually outlined the left and right hippocampal formations using published criteria. They used 3D structural shape analysis methods developed at the Laboratory of Neuro Imaging (LONI) to compare regional variation in hippocampal diameter between the AD cases and the non-demented comparison group. Mean total hippocampal volume was 11.5% smaller in the AD cases than the non-demented controls (4903±857 mm^3 *vs* 5540±805 mm^3), with a similar size difference for the median left (12.0%) and median right (11.6%) hippocampus. Shape analysis showed a regional pattern of shape difference between the AD and non-demented hippocampus, more evident for the hippocampal body than the head, and the appearance of more consistent differences in the left hippocampus than in the right. While assignment to a specific sub-region is not possible with this method, the surface changes primarily intersect the area of the hippocampal body containing the CA1 region (and adjacent CA2 and distal CA3), subiculum, and the dentate gyrus-hilar region.

Apostolova *et al*. [22], using an innovative surface-based hippocampal analytic technique, analyzed the structural MR hippocampal data of 31 aMCI and 34 AD subjects. They tested the hypothesis that AD subjects have greater atrophy of the CA1, CA2 and CA3 hippocampal subfields relative to aMCI subjects. 3D hippocampal maps localized the main group differences to the CA1 region bilaterally and the CA2 and CA3 region on the left [corrected] (right [corrected] P = 0.0024, left [corrected] P = 0.0002, both corrected for multiple comparisons). Age, race, gender, education and Mini-Mental State Examination (MMSE) were significant predictors of hippocampal volume. Hippocampal volume was a significant predictor of clinical diagnosis. Their study suggests that as AD progresses, subregional hippocampal atrophy spreads in a pattern that follows the known trajectory of neurofibrillary tangle dissemination. In this work, state-of-the-art 3D hippocampal analysis techniques allowed to demonstrate selective subregional hippocampal atrophy *in vivo* [23, 37].

Moreover, Apostolova *et al*. [14] investigated the structural neuroimaging correlates of MMSE performance in patients with clinical and preclinical AD. They analyzed structural MRI data from 29 probable AD and 5 MCI patients who later converted to probable AD by using an advanced 3D cortical mapping technique. MMSE scores were entered as covariates in a general linear model that predicted the gray matter density at each cortical surface point. The results were corrected for multiple comparisons by permutation testing. The global permutation-corrected significance for the maps linking gray matter loss and cognitive decline was P=0.005 for the left and P=0.012 for the right hemisphere. Strongest correlations between MMSE score and gray matter integrity were seen in the entorhinal, parahippocampal, precuneus, superior parietal, and subgenual cingulate/orbito-frontal cortices. Significant correlations were also seen bilaterally in the temporal, the middle frontal and the left angular and supramarginal gyri. As a global cognitive measure, MMSE depends on the integrity of widely distributed cortical areas in both brain hemispheres with left-sided predominance.

The purpose of [82] was to determine whether a similar deformity of the hippocampus can predict the onset of dementia in non-demented elders. Using high dimensional diffeomorphic transformations of a neuroanatomical template, hippocampal volumes and surfaces were defined in 49 non-demented elders; the hippocampal surface was subsequently partitioned into three zones (i.e., lateral, superior and inferior-medial), which were proximal to the underlying CA1 subfield, CA2-4 subfields plus dentate gyrus, and subiculum, respectively. Annual clinical assessments using the CDR, where CDR 0 indicates no dementia and CDR 0.5 indicates very mild dementia, were then performed for a mean of 4.9 years (range 0.9-7.1 years) to monitor subjects who converted from CDR 0 to CDR 0.5. Inward variation of the lateral zone and left hippocampal volume significantly predicted conversion to CDR 0.5 in separate Cox proportional hazards models. When hippocampal surface variation and volume were included in a single model, inward variation of the lateral zone of the left hippocampal surface was selected as the only significant predictor of conversion. The pattern of hippocampal surface deformation observed in non-demented subjects who later converted to CDR 0.5 was similar to the pattern of hippocampal surface deformation previously observed to discriminate subjects with very mild AD and non-demented subjects. These results suggest that inward deformation of the left hippocampal surface in a zone corresponding to the CA1 subfield is an early predictor of the onset of AD in non-demented elderly subjects.

The aim of [24] was to locate *in vivo* the structural changes within the hippocampal formation in AD patients of mild to moderate severity. A group of 28 AD patients and 40 cognitively intact persons (age 74 ± 9 and 71 ± 7 years) underwent T1-weighted high-resolution MR scans. The hippocampal formation was isolated by manually tracing on 35 coronal slices the outlines of the proper hippocampus and subiculum after registration to a common stereotactic space. Group differences were assessed with *ad-hoc* developed algorithms that make use of 3D parametric surface mesh models. In AD patients, significant atrophic changes amounting to tissue loss of 20% or more were found in regions of the hippocampal formation corresponding to the CA1 field and part of the subiculum. Regions corresponding to the CA2-3 fields were remarkably spared. The regions of the hippocampal formation that were found atrophic in AD patients are those known to be affected from pathological studies. This study supports the possibility of carrying out *in vivo* macroscopic neuropathology of the hippocampus with MRI in the neurodegenerative dementias.

Thomson *et al*. [37] developed an anatomical mapping technique to detect hippocampal and ventricular changes in AD. The resulting maps are sensitive to longitudinal changes in brain structure as the disease progresses. An anatomical surface modeling approach was combined with surface-based statistics to visualize the region and rate of atrophy in serial MRI scans and isolate where these changes link with cognitive decline. Sixty-two high-resolution MRI scans were acquired from 12 AD patients (mean age ± SE at first scan: 68.7 ± 1.7 years) and 14 matched controls (age: 71.4 ± 0.9 years) each scanned twice (1.9 ± 0.2 years apart). 3D parametric mesh models of the hippocampus and temporal horns were created in sequential scans and averaged across subjects to identify systematic patterns of atrophy. As an index of radial atrophy, 3D distance fields were generated relating each anatomical surface point to a medial curve threading down the medial axis of each structure. Hippocampal atrophic rates and ventricular expansion were assessed statistically using surface-based permutation testing and were faster in AD than in controls. Using color-coded maps and video sequences, these changes were visualized as they progressed anatomically over time. Additional maps localized regions where atrophic changes linked with cognitive decline. Temporal horn expansion maps were more sensitive to AD progression than maps of hippocampal atrophy, but both maps correlated with clinical deterioration. These quantitative, dynamic visualizations of hippocampal atrophy and ventricular expansion rates in aging and AD may provide a promising measure to track AD progression in drug trials.

Other Cerebral Areas

Most studies have focused on sub-cortical structures, and especially the hippocampus, regarding their crucial roles in higher cognitive functions and memory processes respectively. Up to now, fewer MRI studies have been performed examining the role of additional temporo-parietal regions, whereas the basal nuclei and thalamus have received even less attention.

Of these studies, some have manually drawn regions of interest within temporo-parietal regions, such as the fusiform and superior temporal gyrus [72, 83]. In addition, others have used whole-brain measures, such as voxel-based morphometry [84-86], fluid registration methods [87, 88], and cortical thickness approaches [89, 90], thus avoiding the need to measure individual anatomic areas. Taken together, the results of these studies provide evidence that areas within the parietal and lateral temporal lobes may additionally be involved in the earliest stages of AD. However, it remains unclear which specific region, or which combination of these regions beyond the MTL, best predicts disease progression from MCI to AD.

In [91] MR images from 129 individuals with MCI were analyzed to identify the volume of 14 neo-cortical and 2 non-neo-cortical brain regions, comprising the temporal and parietal lobes. In addition, 3 neuropsychological test scores were included to determine whether they would provide independent information. After a mean follow-up time of 5 years, 44 of these individuals had progressed to a diagnosis of AD. Cox proportional hazards models demonstrated significant effects for 6 MRI regions with the greatest differences being the following: the entorhinal cortex (hazard ratio [HR]=0.54, $P < 0.001$), inferior parietal lobule (HR = 0.64, $P < .005$), and middle temporal gyrus (HR = 0.64, $P < .004$), indicating decreased risk with larger volumes. A multivariable model showed that a combination of the entorhinal cortex (HR = 0.60, $P < .001$) and the inferior parietal lobule (HR = 0.62, $P < .01$) was the best predictor of progression to AD, and reiterated the importance of including both MRI and neuropsychological variables. These findings confirm the importance of the entorhinal cortex and of the inferior parietal lobule as predictors of progression in time from MCI to AD. The inclusion of neuropsychological performance in the final model continues to highlight the importance of using these measures in a complementary fashion.

de Jong *et al*. [92], besides confirming the well known presence of decreased global grey matter and hippocampal volumes in AD, investigated whether deep grey matter structures also suffer degeneration in this syndrome, and whether such degeneration is associated with cognitive deterioration. In this cross-sectional correlation study, two groups were compared on volumes of seven sub-cortical regions: 70 memory complainers (MCs) and 69 subjects diagnosed with probable AD. Using 3 Tesla 3D T1 MR images, volumes of nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen and thalamus were automatically calculated by means of the Integrated Registration and Segmentation Tool (FIRST) algorithm, developed at the Oxford Centre for Functional MRI of the Brain (FMRIB). Subsequently, the volumes of the different regions were correlated with cognitive test results. Besides finding the expected association between hippocampal atrophy and cognitive decline in AD, volumes of putamen and thalamus were found to be significantly reduced in patients diagnosed with probable AD. Moreover the decrease in volume correlated linearly with impaired global cognitive performance. These findings strongly suggest that, beside sub-cortical atrophy, deep grey matter structures in AD suffer atrophy as well and that degenerative processes in the putamen and thalamus, in the same way as the ones in the hippocampus, may contribute to cognitive decline in AD.

CONCLUSIONS

The importance of this entire field is to increase by several orders of magnitude as soon as a treatment capable of slowing the progression of AD is identified and announced. Several clinical treatment trials are coming to a close (results not yet announced), and many more are being planned. The implications then become obvious and huge, and encompass the way in which neuroimaging techniques might assist in making the diagnosis of AD and distinguishing it from other dementias; the role of the neuroradiologist in diagnosing dementia in its early stage; the role of automated segmentation and registration programs for improved diagnosis; and finally, the identification of those subjects who, cognitively healthy at present, are at high risk of developing AD in the future.

We should take advantage of all of the rapidly improving technologies of MRI acquisition (structural, perfusional, diffusion tensor, susceptibility weighted MRI and magnetic resonance spectroscopic imaging), reconstruction (Fourier

and Bayesian methods), and image processing (segmentation and registration) techniques to address these fascinating and very high-impact medical questions.

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