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Estimation of Hippocampus Volume from MRI Using ImageJ for Alzheimer's Diagnosis

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Abstract

In an effort to aid the Alzheimer's diagnostic arena, this study aims to help differentiate the Medical Imaging Techniques available for predicting the onset of Alzheimer's disease (AD). Despite practical limitations set by medical imaging policies, neuroimaging proves promising in early detection today as some volumetric studies have focused on the atrophy of the hippocampus as a major marker of the disease. These preliminary findings promote the efforts to establish an AD diagnostic algorithm for clinical use enabling for less expensive diagnoses to deliver earlier treatment maximising the benefit and quality of life of an Alzheimer's victim. In this paper we have made an attempt to analyse three major medical imaging techniques which are associated with AD, namely CT, PET, and MRI. We found that MRI is more beneficial than the others and present a convenient and easy mechanism to estimate hippocampal atrophy using ImageJ, which is an indication of the presence of AD.

Keywords: Medical imaging, Alzheimer's disease, diagnosis, ImageJ, atrophy

Introduction

Dementia is a generic term that describes the cognitive decline in brain function. Some conditions that cause dementia can be reversed, and others cannot. The two most common forms of dementia in older people are Alzheimer's disease and multi infarct dementia (sometimes called vascular dementia). These types of dementia are irreversible. Alzheimer's disease (AD) is the most common form of dementia; it accounts for 64 per cent of all dementias. AD is characterised by a progressive decline in cognitive function. AD usually affects people over the age of 65 years, with a progressive decline in memory, thinking, language and learning capacity. AD should be differentiated from normal age-related decline in cognitive function, which is more gradual and associated with less disability. AD often starts with mild symptoms and ends with severe brain damage. People with dementia lose their abilities at different rates.

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), and the Alzheimer's Disease and Related Disorders Association (ADRDA) defines Alzheimer's disease as a progressive, degenerative disorder that attacks the brain's nerve cells, or neurons, resulting in loss of memory, thinking and language skills, and behavioural changes.

AD is a neurodegenerative disease that ravages its victims'

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memory to affect their learning, cognitive, and communicative abilities. Alzheimer's disease (AD) affects the central nervous system and begins in middle to late life, and results in severe dementia and ultimately death. It is the fourth major cause of death after heart diseases, cancer and stroke. As awareness grows, more and more old people earlier assumed to be afflicted by other diseases are now being diagnosed as suffering from AD. The demographic data show that presently there are about 18 million people in the world with dementia. Approximately 70% of this number is contributed by the developing countries. The projected estimate for Europe alone is about eight million and for United States about four million AD patients. Epidemiological information from India is rather scanty. Satishchandra et al. (1997) reported the first case of familial AD (FAD) in India. Another study carried out in Kerala found 66 cases of dementia among 2,067 persons over the age of 60 years, a prevalence rate of 3.2%. Out of this, 58% had vascular type while 41% had Alzheimer's type dementia. Surveys conducted in Tamil Nadu and other parts of India also suggest that Indians are as prone to dementia as other ethnic groups. Considering India's 70 million elderly population and increasing life expectancy above 60, the number of AD cases is expected to go up and demands for the healthcare of people with dementia will rise remarkably in the new millennium.

The management cost of AD is huge and it becomes an enormous social and economic burden on support services. Therefore, AD is an intellectually challenging and socially important problem for healthcare of the elderly. Its importance has recently attracted the attention of scientists and social workers due to ever-increasing proportion of the elderly population throughout the world. There is an urgent need for early diagnosis of the disease.

Current Diagnostic Tests

Coexisting medical problems may cause or contribute to cognitive impairment. The patient's medical history and findings on physical examination should direct diagnostic evaluation. In general, most patients should undergo a complete blood count; thyroid function screening; and routine blood studies for liver, kidney, and endocrine function. Most dementia specialists also obtain a serum vitamin B12 level, which may be low despite the absence of anaemia or macrocytosis. However, although mild cognitive impairment has improved after treatment with vitamin B12, there is no evidence of beneficial effect (either an improvement in cognitive function or a halt in the progressive downhill course of the disease) in patients who have already progressed to dementia at the time of treatment.

Current MCI and AD diagnostic practices require evident cognitive and memory impairment affecting daily function. Cognitive states are assessed using neuro-psychiatric examinations such as the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), and are the only means of detecting dementia. However these tests are limited.

Consequently, in an effort to reliably and pre-symptomatically discriminate MCI from AD, neuroimaging technology has entered the diagnostic arena. Studies ranging from the usage of Positron Emission Tomography (PET) to magnetic resonance (MR) imaging have focused on the functional activity, morphometrics, or volumetrics of various regions of interest (ROIs). These studies have found consistent and supportive effects of atrophy as a function of time in various medial temporal lobe structures in the early pathological progression from MCI to AD. The ability to discriminate MCI from AD enables the potential rescue of the patient's quality of life and memory granted the availability of treatment. Specific studies have been successful in volumetrically differentiating and identifying the hippocampus as the biostructural marker for early progression into AD, marking distinct atrophy rates in these structures for usage and confirmation of diagnosis, thus substantiating the diagnostic usage of neuroimaging (specifically MRI).

Medical Imaging in Alzheimer's Disease

Initially, approaches to AD imaging were faced with major obstacles in all the essentials of credible study: sensitivity, specificity, and reproducibility. These earliest studies on AD imaging that were based on pneumoencephalography, and even later studies with CT or MRI, focused mainly on two different approaches. One was to evaluate conventional brain atrophy, the other to evaluate changes in the white matter.

Computed Tomography and Evaluation of Brain Atrophy

Previous CT studies, and even some more recent MR studies, have focused on the evaluation of gross brain atrophy in AD. These studies are foremost based on assessing the dilatation of various ventricular and subarachnoidal spaces, and the enlargement of sulci, using linear measurements and indices, planimetry, or volumetry. In fact, few studies applying CT have been able to classify up to 90% of AD patients and control subjects correctly. In these studies, the best results have been obtained by longitudinal follow-up, demonstrating an accelerated rate of volumetric atrophy.

The face value of these measurements, however, must be criticised as somewhat questionable, because gross brain atrophy may occur in normal elderly without any neurological or other deficits whatsoever, and may therefore be regarded as "physiological atrophy". Therefore, in early AD most CTs appear normal, or close to normal, and do not differentiate AD from normal aging or other neurodegenerative or neuropsychiatric disorders that might clinically resemble AD. Also, the qualitative interpretation of these findings has often lacked reproducibility. Moreover, detailed imaging of the temporal lobes in conventional axial CT images is virtually impossible due to beam hardening artefacts. These findings gathered strongly restrict the use of CT as a true and reliable diagnostic tool for AD.

PET Scans

Clinical studies have demonstrated that Positron Emission Tomography (PET) scans may be the most accurate method of diagnosing Alzheimer's disease, particularly in its early stages.

PET scans show a characteristic diagnostic pattern for Alzheimer's disease, where certain regions of the brain have decreased metabolism early in the course of the disease. Early detection and confirmation of Alzheimer's disease permits drug therapy to slow the loss of a patient's ability to function. A diagnostic test for Alzheimer's disease is also valuable in helping to counsel patients, caregivers, and families, thus enabling them to cope with this condition more effectively. PET scans may also reassure fearful patients who might not have the disease, or redirect treatment for other conditions associated with dementia.

MRI Imaging

The recent development of MRI has offered new insights and possibilities into the field of neuroimaging. In this field, MRI shows superior anatomic accuracy compared to computed tomography (CT) or perfusion imaging methods (positron emission tomography, PET; single photon emission computed tomography, SPECT). MRI non-invasively provides both quantitative and qualitative data of in vivo tissue.

According to a study published in the Journal of the American Medical Association, researchers are exploring whether the use of MRI and other imaging methods may be expanded to play a more direct role in diagnosing Alzheimer's. Recent research indicates that high-resolution structure imaging (MRI) and functional imaging (fMRI, PET) can detect changes that are predictive of Alzheimer's. These studies may lead to new diagnostic approaches for mild cognitive impairment and early Alzheimer's in the next few years.

The Alzheimer Research Forum goes on to say that current research studies indicate that tissue loss associated with very early Alzheimer's can be detected by MRI, even before cognitive symptoms have become observable. Thus, MRI could become an important tool in identifying individuals who can benefit from treatment to delay disease progression. Another promising area of functional imaging research focuses on developing tracer compounds that will attach to key abnormal brain deposits implicated in Alzheimer's.

MRI is generally regarded as a superior tool for brain imaging, as compared with CT, due to the absence of ionising radiation, increased imaging flexibility, and better tissue contrast. Unfortunately, expense, patient claustrophobia, or the presence of metal implants or medical devices common in older individuals can limit the use of MRI.

In this study, some approaches to MRI of the hippocampus are evaluated. First, the whole volume of the hippocampus is measured. In order to obtain data as precise and reliable as possible, the volumes are measured using thin, contiguous, optimally oriented image slices in a substantial number of well- controlled study subjects. A 1.5 T imager, which makes highly accurate imaging possible, is used in the study.

Imaging of the AD Hippocampus

Several studies have tried to evaluate both normal anatomy and pathology of the hippocampus and its possible use for diagnostic purposes, with results varying vastly depending upon the study setting. The use of imaging planes oriented perpendicular to the long axis of the hippocampus, combined with optimal imaging parameters (heavily T1-weighted) that maximise grey/white matter contrast, have made measurements of the entire hippocampus, including the anterior part, not only feasible, but also reliable and reproducible (Jack et al., 1992). In normal subjects, several studies have reported the hippocampus to be larger on the right than on the left (Watson et al., 1992; Soininen et al., 1995; Zipursky et al., 1994).

Among the first MRI studies on AD hippocampus, Seab et al. (1998) detected the hippocampal area to be reduced by 49%, with no overlap between ten AD patients and seven control subjects. In 1991, Kesslak et al. (1991) found a similar reduction of 48.8% in hippocampal volume in eight AD patients compared to seven age-matched controls. In the same year, Dahlbeck et al. (1991) introduced a variable called interuncal distance (IUD). The IUD was presented as a simple diagnostic method for AD, obtainable from a single slice on an MR scan. Widening of IUD was considered to reflect hippocampal atrophy, and it was proposed that an IUD of 30 mm or more would suggest the presence of AD. Later, normative data for IUD supported the hypothesis that in normal control subjects the IUD is not likely to exceed 30 mm (Doraiswamy et al., 1993).

In the study of Jack et al., 85% of the hippocampal volumes in early AD patients fell below those of controls. Pearlson et al. (1992) found the area of the AD hippocampus being approximately 60% of the area in controls. Scheltens et al. (1992) reported a discriminating sensitivity of 81% by visual assessment of the hippocampus and temporal lobe. Later this result was reported to correlate significantly with volumetric atrophy (Vermersch et al., 1994).

In 1993, Killiany et al. were able to correctly identify 100% of the controls and the early AD group in a discriminant function analysis including a combination of volumes of the hippocampus and temporal horn of the lateral ventricle (Killiany et al., 2000).

MRI Technique for Volumetric Studies

The imaging of the normal aging brain is an important issue, both for an in vivo regular anatomical presentation of the brain, and for the changes that are related to it. Neuropathological studies have revealed changes in the brain with advancing age. There is a constant hemisphere volume in individuals between the ages of 20 and 50 years, but thereafter there is a decrease in volume of 2% per decade. Thus, after the age of 50, the brain size suffers from increasing atrophy with age, but different studies have reported changes in the brain connected with the process of maturisation of the brain during its life span: both global and selective decreases in cortical volume and an increase in ventricular volume have been detected in MRI studies (Mann et al., 1991; Regeur et al., 1994; Hubbard et al., 1981; Salat et al., 2009).

Data from standard anatomical atlases of the human brain were used as guidelines to determine the boundaries of the hippocampus in MRI.

Materials and Methods

Hippocampus volumes can be accurately calculated from magnetic resonance imaging (MRI) scans. Hippocampus volumetry is useful for Alzhemier diagnosis and helps reduce the incidence of complications . Unfortunately, radiologic image analysis software is typically linked to radiologic hardware, making it less accessible for non-radiologists. In addition, the intended operation should be known to the investigator to predict the hippocampus volume accurately. This requires the expertise of dedicated surgeons and radiologists. Advances in digitalisation, the availability of broadband networks, and the introduction of MRI scans on CD-ROM have enabled volumetry on a personal computer remote from radiological hardware (CT scanners or MRI). Advantages of standalone software are its applicability for tertiary referred patients, who already have a proper CT scan on CD-ROM from the referring institution and the possibility of performing hippocampus volumetry independent of the input of a radiologist. However, commercially available stand-alone volumetry software is often expensive. Recently, an alternative approach using Adobe® Photoshop® was proposed to circumvent this problem, but the method is laborious. ImageJ is a freely downloadable image analysis software package developed at the National Institute of Health (NIH) to assist in clinical and scientific image analyses. The applicability of ImageJ for hippocampus volumetry has not been addressed before, but it potentially brings hippocampus volumetry to the surgeon's desktop. The objective of the present study was to establish the accuracy of ImageJ for MRI volumetric analysis of the hippocampus on a personal computer.

The subjects used for this study were scanned with a 1.5 T Magnetom (Siemens, Erlangen) resulting in contiguous T1 weighted partitions with a slice thickness of 1.0-5.0 mm oriented perpendicular to the long axis of the hippocampus. A substantial number of patients admitted are referred from district general hospitals of Tamil Nadu. In our experience most of these patients already have a proper MRI scan on CD-ROM from the referring institution. In most of these cases, however, it would not be possible to perform volumetry on these scans owing to incompatibility between radiological software packages. ImageJ eliminates the necessity to perform an additional scan for the sole purpose of volumetry.

Calculation of Hippocampus Volume Using ImageJ

Step 1 Downloading ImageJ Software - ImageJ (version 1.33) was downloaded from http://www.rsb.info.nih.gov/ij/download.html.

Step 2 Creating a Stack - Relevant MRI slices were evaluated in the original viewer called Syngo FastView from Siemens AG Medical Solutions,UK. The software is downloadable from http://download.cnet.com/syngo-fastView/3000-2056_4-10672039.html (manufacturer, location? Is it syngo FastView?). Every MRI slice has a unique code or number that can be found in the information menu of the viewer, matching a JPEG file. The JPEG files were retrieved with Windows® Explorer and opened in ImageJ by dragging them to the ImageJ main window. Individual slices were transformed into a "stack" using the function "Convert Images to Stack" found in submenu "Stacks" (Fig. 1).

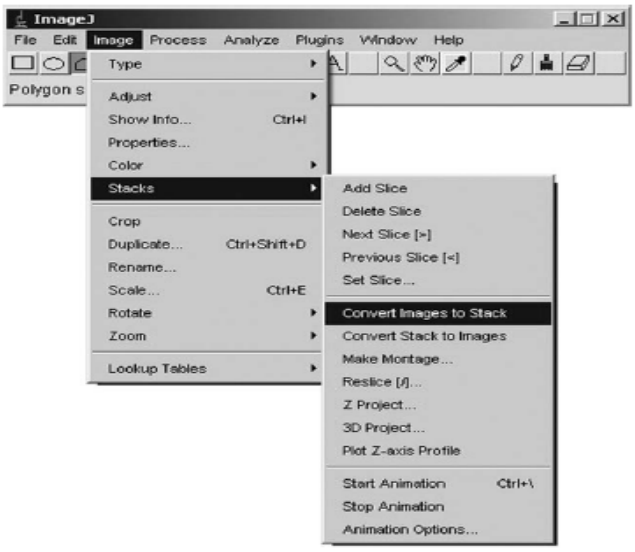

Fig. 1. Creating a stack using "Convert Images to Stack" function.

Step 3 Adjusting Scale - After opening DICOM images in ImageJ, the scaling of the images is corrected automatically, and volumetric analysis can be continued. However, in non-DICOM viewers, the scale of the imported stack was adjusted by measuring the distance between two randomly chosen but clearly recognisable points on a slice in the original viewer using its measurement tool. Subsequently, the line between these points was traced on the corresponding slice and its distance set in ImageJ using the "Set scale" function in the "Analyse" submenu.

Step 4 Creating a Region of Interest - On the MRI slices, the region of interest (ROI) relevant for the present study is the hippocampus. Before outlining the ROI on each slice, the ROI manager in the pull-down menu "Analyse > Tools" was opened. The right and left hippocampus were manually outlined using the "Polygon selection tool". This tool can create an irregularly shaped selection defined by a series of line segments. To create an ROI on the MRI slice, the mouse has to be clicked repeatedly to create line segments. When finished, one has to click in the small box at the starting point, and ImageJ automatically draws the last segment. The respective ROI of each slice was added to the ROI manager with the function "Add" in the ROI manager menu.

Step 5 Calculating Volume - To calculate the areas, all the ROIs must be selected in the ROI manager. The area of each ROI was calculated with the function "Measure" in the ROI manager menu (Figure 2). The calculated areas were then selected and copied (right click) to Microsoft® Excel, where the areas were multiplied with slice thickness (ranging from 1.0 to 5 mm, varying per viewer and/or patient). The last step was to add up these values per slice and calculate the volume of each three-dimensional structure. The data

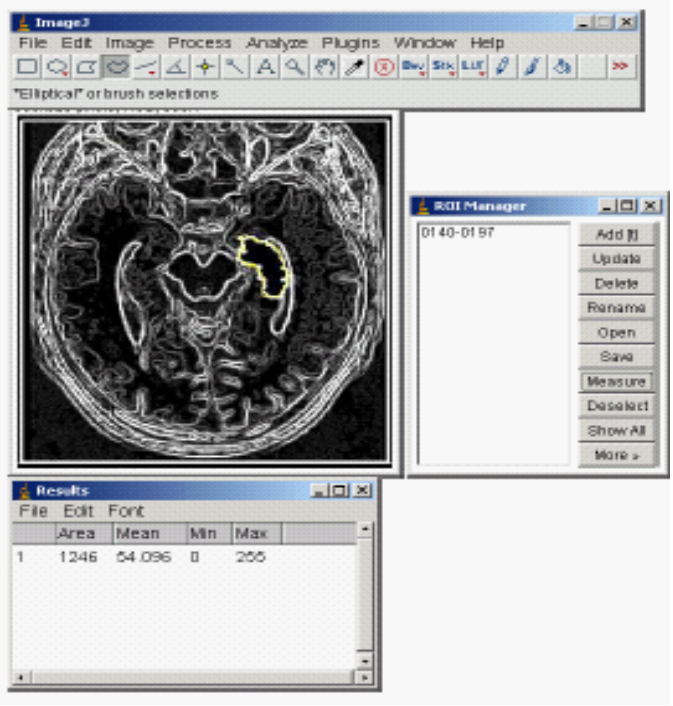

Fig. 2. Calculating area using the "Measure" function.

are then presented in cubic centimetres. Subsequently, these values per slice were added up to calculate the volume of each three-dimensional structure.

Results and Discussion

Normalised hippocampal volumes were 1.95 cm^3 ± 0.46 (range: 0.98-3.10) for AD patients, 2.30 cm^3 ± 0.46 (1.28-3.10) for MCI patients and 2.86 cm3 ± 0.46 (1.74-4.05) for control participants. Significant hippocampal volume reductions were found in both AD (-32% (0.91 cm^3/2.86 cm^3) volume reduction,) and MCI patients (-19% (0.56 cm^3/2.86 cm^3) volume reduction), compared to elderly controls (Table 1). AD patients also had significantly smaller hippocampus compared to MCI patients (-15% (0.35 cm^3/2.30 cm^3) volume reduction, $p<0.01$).

The results showed that there were no significant differences in the volumes calculated by the operator and the automated one proposed in the study. The study also showed that automated segmentation was able to detect significant volume differences in both AD patients and patients with MCI. The results are in concordance with a vast number of studies based on manual hippocampal segmentation which have shown hippocampal atrophy in patients with Alzheimer's disease and in patients with MCI. Compared to elderly controls, we found an average 32% hippocampal volume loss in patients with AD. This value is in the range of those reported studies used in manual volumetry, with volume loss comprising between 23% and 34%. In patients with MCI, values ranged from 8% to 15%.

Table 1. Comparison between manual and automated hippocampus volume calculation.

	Normalised Hippocampal volume (cm^3)	Volume Reduction (%)
AD vs controls	1.95 vs 2.86	32% ($p < 0.001$)
MCI vs controls	2.30 vs 2.86	19% ($p < 0.001$)
AD vs MCI	1.95 vs 2.30	15% ($p < 0.01$)

Conclusion

The causes of Alzheimer's disease remain enigmatic. One of the goals of modern neuroimaging is to help in the early and accurate diagnosis of Alzheimer's disease, which can be challenging. The advantage of this procedure is that volumetry can be done by the surgeon without support from the radiology department. Time efficiency can be further improved by downloading a volume measurement "plug-in" that calculates the volume directly in the ROI manager. This eliminates the extra step of exporting calculated areas to Microsoft® Excel. The plug-in can be downloaded for free. When the disease is diagnosed early, drug treatment can help improve or stabilise patient symptoms.

References

Satishchandra P, Yasha TC , Shanka L, et al. Alzheimer's disease and associated disorders. Current Science 1997; 11: (107-109).

Jack CR Jr, Petersen RC, O'Brien PC et al. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. Neurology 1992; 42:183-8.

Watson C, Andermann F, Gloor P et al. Anatomical basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology 1992;42:1743-1750.

Soininen H, Partanen K, Pitkänen A et al. Decreased hippocampal volume asymmetry on MRIs in nondemented elderly subjects carrying the apolipoprotein E 4 allele. Neurology 1995;445:391.

Zipursky RB, Marsh L, Lim KO, et al. Volumetric MRI assessment of temporal lobe structures in schizophrenia. Biol Psychiatry 1994;35:501-516.

Seab JP, Jagust WJ, Wong STS et al. Quantitative NMR measurements of hippocampal atrophy in Alzheimer's disease. Magn Reson Med 1988;8:200-208.

Kesslak JP, Nalcioglu O, Cotman CW. Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. Neurology 1991;41:51-54.

Dahlbeck SW, McCluney KW, Yeakley JW et al. The interuncal distance: A new MR measurement for the hippocampal atrophy of Alzheimer's disease. AJNR 1991;12:931-932.

Doraiswamy PM, McDonald WM, Patterson L et al. Interuncal distance as a measure of hippocampal atrophy: normative data on axial MR imaging. AJNR 1993;14:141-143.

Pearlson GD, Gordon JH, Powers RE et al. Quantitative changes in mesial temporal volume, regional cerebral blood flow, and cognition in Alzheimer's disease. Arch Gen Psychiatry 1992;49:402-408.

Scheltens Ph, Leys D, Barkhof F et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992;55:967-972.

Vermersch P, Leys D, Scheltens P et al. Visual rating of hippocampal atrophy: correlation with volumetry (a letter). J Neurol Neurosurg Psychiatry 1994;57:1015.

Killiany RJ, Teresa GI et al., Use of structural magnetic resonance imaging topredict who will get Alzheimer's disease. 2000,Ann Neurol 47:430–439.

Mann DMA. The topographic distribution of brain atrophy in Alzheimer's disease. Acta Neuropathol (Berl) 1991; 83: 81–86.

Regeur L, Jensen GB, Pakkenberg H, Evans SM, Pakkenberg B. No global neocortical nerve cell loss in brains from patients with senile dementia of Alzheimer's type. Neurobiol Aging 1994; 15: 347–352.

Hubbard BM, Anderson JM. A quantitative study of cerebral atrophy in old age, and senile dementia. J Neurol Sci 1981; 50: 135–145.

Salat D.H., Greve D.N., Pacheco J.L.,et al, Regional white matter volume differences in nondemented aging and Alzheimer's disease , NeuroImage,2009, 44 (4), pp. 1247-1258.

Petersen RC, Jack CR Jr. Memory and MRI-based hippocampal volumes in aging and AD. Neurology 2000; 54:581-586.

Henneman WJP, Sluimer JD, Cordonnier C et al. MRI Biomarkers of Vascular Damage and Atrophy Predicting Mortality in a Memory Clinic. Population Stroke 2009; 40(2): 492-498.

Van de Pol LA, , Korf ESC,, van der Flier WM, et al. Magnetic Resonance Imaging Predictors of Cognition in Mild Cognitive Impairment. Arch Neurol July 1, 2007; 64(7): 1023-1028.

Slavin MJ, Sandstrom CK, Tran TTT et al. Hippocampal Volume and the Mini-Mental State Examination in the Diagnosis of Amnestic Mild Cognitive Impairment. Am J Roentgenol May 1, 2007; 188(5): 1404-1410.

Apostolova LG, Dutton RA, Dinov ID et al. Conversion of Mild Cognitive Impairment to Alzheimer Disease Predicted by Hippocampal Atrophy Maps. Arch Neurol May 1, 2006; 63(5): 693-699.

Modrego PJ, Fayed N, and Pina MA. Conversion From Mild Cognitive Impairment to Probable Alzheimer's Disease Predicted by Brain Magnetic Resonance Spectroscopy. Am J Psychiatry April 1, 2005; 162(4): 667-675.

Rusinek H, De Santi S, Frid D et al. Regional Brain Atrophy Rate Predicts Future Cognitive Decline: 6-year Longitudinal MR Imaging Study of Normal Aging, Radiology December 1, 2003; 229(3): 691-696.

Adachi M, Kawakatsu S, Hosoya T et al. Morphology of the Inner Structure of the Hippocampal Formation in Alzheimer Disease. AJNR Am J Neuroradiol September 1, 2003; 24(8): 1575-1581.

Resnick SM, Pham DL, Kraut MA et al. Longitudinal Magnetic Resonance Imaging Studies of Older Adults: A Shrinking Brain. J Neurosci April 15, 2003; 23(8): 3295-3301.

Smith AD. Imaging the progression of Alzheimer pathology through the brain. PNAS April 2, 2002; 99(7): 4135-4137.

Sencakova D, Graff-Radford NR, Willis FB et al. Hippocampal Atrophy Correlates with Clinical Features of Alzheimer Disease in African Americans. Arch Neurol October 1, 2001; 58(10): 1593-1597.

Hsu YY, Schuff N , Du AT et al. Comparison of automated and manual MRI volumetry of hippocampus in normal aging and dementia J Magn Reson Imaging 2002;16(3): 305-310.

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