行政院國家科學委員會專題研究計畫 成果報告

以磁振影像體積和擴散測量技術應用於阿茲海默氏症之長期研究

研究成果報告(精簡版)

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INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly and affects more than 30 million individuals worldwide. The progression of AD is gradual, and the average patient lives 8-10 years after onset of symptoms. Thus, with the growth of the older population in developed nations, the prevalence is expected to triple over the next 50 years [1]. In the United States, The annual cost of the disease, including medical, long-term, and home care, as well as loss in productivity, is currently estimated at US$100 billion [2]. Not only is the financial burden substantial, but the psychological and emotional burden on patients and their families is even greater.

The purpose of this study is to investigate brain atrophy progression and integrity of white matter tracts in both mild cognitive impairment (MCI) and AD by serial MRI, which includes high resolution T1 weighted images and diffusion tensor images, and also to build up an image database for further AD studies in the central area of Taiwan. It is also important to have the database which includes serial images of the elderly and their corresponding detailed neuropsychologic assessments, and it helps us to understand the progression of the disease and the correlation in image findings.

Authors of a number of initial studies describing MR-based volume measurement reported high sensitivity in distinguishing patients with AD from elderly control subjects. However, many of these studies were flawed by imaging methods, by variations in neuroanatomic boundary criteria, and by small and highly selected samples, which made extrapolation to diagnosis of AD in a general setting problematic [3]. Serial measurements may be more specific than single measurements for detecting differences between patients with AD and control subjects. Rates of hippocampal atrophy have correlated with cognitive status at baseline and with change in cognitive status over time. Jack et al [4] studies 22 subjects with probable AD and 22 age-matched control subjects. The annualized rate of hippocampal atrophy and temporal horn enlargement was approximately two times greater in patients with AD. A more recent study [5] with grouped according to probable AD, MCI, and age-matched control has been shown that the rates of hippocampal atrophy lie along a continuum from patient with AD to those with MCI to age-matched control subjects.

In diffusion tensor study, the presence and extent of white matter alterations could be as possible correlate of impaired memory function and as predictor of progression to AD. The ultrastructural integrity of white matter tracts can be revealed by diffusion tensor imaging, and, therefore, the pathological processes that modify tissue integrity can be detected as well [6]. The longitudinal study for diffusion tensor imaging is also important in MCI patients, since it could trace the white matter degeneration before the significant cognitive decline appeared. Furthermore, the fiber tracking technique is useful for evaluation the white matter tract integrity visually.

METHODS

Subjects Recruitment and Scans

Subjects with MCI and with AD were recruited. For all subjects, a history was taken and a physical examination was performed. Cognitive function of the subjects was measured with detailed neuropsychologic assessments and the Cognitive Abilities Screening Instrument (CASI) [7]. In addition,

age-matched healthy subjects with no complaints of cognitive problems and no evidence of memory deficits on formal tests were recruited from volunteers.

All subjects underwent MR imaging and one or more repeat studies every six months to monitoring the changes in imaging findings and the corresponding cognitive decline. After the subject being measured with detailed neuropsychologic assessments and the CASI, coronal T1-weighted images and axial diffusion tensor images were acquired in a 1.5T MR system. For T1-weighted images, fast SPGR with IR prepared (α /TI/TR/TE=15/400/12.2/4.2) was employed with 124 1.5-mm thick slices to cover the whole brain. The SE-EPI (TR/TE=10000/50) with diffusion gradients applied in different directions was performed to obtain the diffusion information.

Image Processing and Data Analysis

The CASI contains nine cognitive domains, attention, concentration, orientation, short-term memory, long-term memory, language ability, visual construction, category fluency and abstraction and judgment. The total score of CASI and the individual scores from each cognitive domain are used to distinguish different level of dementia [8].

For each brain volume image, volumetric measures of the gray matter, white matter, ventricles, hippocampus, entorhinal cortex, amygdala, cingulated gyrus, frontal and temporal lobes, and whole brain were performed by techniques of region of interest (ROI) analysis, and image segmentation [9, 10]. The volumetric measurements of different brain tissues are normalized by the whole brain volume to remove subject-related effects. The small structures, such as hippocampus, entorhinal cortex, and amygdale are manually chosen according to the protocol published by Bonilha et al [11], and the volume measurements are performed by the home-made MATLAB programs.

Diffusion tensor imaging reveals the structural integrity of white matter tracts. Therefore, it is very useful to detect pathological processes that modify tissue integrity in patients with MCI and AD. The diffusion weighting MR images are employed to create apparent diffusion coefficient maps along each direction as well as off-diagonal elements of the diffusion tensor matrix. Mean diffusivity (MD) and fractional anisotropy (FA) were further computed from the diffusion tensor matrix. Then, MD and FA were measured in temporal, frontal, parietal and occipital white matter regions. Other small structures, such as hippocampus and corpus callosum, MD and FA are measured as well.

The diffusion weighted images are acquired in SE-EPI with strong diffusion gradient applied. Since the SE-EPI sequence is very sensitive to off-resonance factors such field inhomogeneity and eddy current which is produced by strong diffusion gradient, the distortion correction algorithm is needed to restore image by removing the geometric distortions. The reason that causes the image distorted is the phase error accumulated in EPI acquisition. Therefore, to remove the distortion, phase correction and phase unwrapping were established.

Brain atrophy and white matter integrity are measured by T1 weighted images and diffusion tensor images, respectively. The image findings are necessary to be compared with the cognitive scores which measured

by CASI. Since CASI provides both total score and nine individual cognitive domain scores to distinguish different level of dementia, the correlation between each CASI scores and image findings will be analyzed.

AD is known to develop slowly. Neuropathological changes have been shown to accumulate for many years, even though cognitive function initially remains normal. The first cognitive deficit in AD is usually an episodic memory impairment. The long preclinical period of AD coupled with the observation that many MCI patients convert to AD within a few years implies that many MCI patients have neuropathology similar to AD. To understand the conversion of MCI to AD, a longitudinal study is required to monitor changes in both images and cognitive measurement every six months.

For serial images acquired from the same subject every six months, image registration techniques are needed to minimize the errors from image positioning at different acquisition time. The registration uses an algorithm that determines the rotations and translations required to minimize the standard deviation (SD) of the ratio between corresponding voxels within brain [12]. The available software, such as Statistical Parametric Mapping (SPM) and/or Automatic Image Registration (AIR), performs alignment automatically as long as proper parameters are set.

To measure brain atrophy, a voxel compression subtraction technique [13] is employed to access serial volume changes in individual subjects. A nonlinear registration algorithm using a compressible viscous fluid model is then applied to track local cerebral losses and deformations, which are presented in the form of a color overlap map on the baseline image. Beside brain atrophy measured in the voxel compression subtraction technique, the volume decrease of hippocampus, entorhinal cortex, amygdala, cingulated gyrus, frontal and temporal lobes will be obtained as well. The coordinate of ROIs, obtained in ROI analysis and segmentation described previously, can be transferred to the realigned coordinate system with the transformation matrix calculated in the realignment process. Then the volume changes are determined by subtracting serial volume images in realignment coordinate.

The serial diffusion images provide the progression of the white matter tracts changes, which is corresponding to the disruption of integrity caused by pathological processes. It can be measured quantitatively by subtracting both serial MD maps and serial FA maps, if these serial maps are properly registered. Therefore, image registration technique is also needed for diffusion measurements.

Intra-subject brain atrophy and white matter integrity change can be measured by serial T1 weighted images and serial diffusion tensor images, respectively. The image findings in the longitudinal study are necessary to be compared with the declines of CASI scores which include the decreasing in both total score and nine individual cognitive domain scores. The statistical analysis between decreasing of CASI scores and changes in both brain volume and whit matter integrity will be performed.

The data analysis in the third year of the longitudinal study is focused on the subjects whose cognitive function significantly declined within three years follow-up. According to the performance of CASI, the subjects' cognitive function declined from MCI to AD will be grouped to compare with other groups

White matter tractographical models will be established from the data base of the serial diffusion tensor images. Fiber tracking is performed using a line propagation technique based on continuous number field [14]. Tracking is launched from a seed voxel from which a line is propagated in both retrograde and antegrade directions according to the principal eigenvector at each voxel.

RESULTS AND DISCUSSION

The items been done in this study are as follows, (a) a part of image database for AD related researches, which includes subjects' detailed neuropsychologic assessments and their corresponding high resolution T1 weighted brain volume images, and diffusion tensor images; (b) programs for ROI analysis and automatic image segmentation for volume measurements; (c) the program for calculating MD and FA from diffusion weighted images; (d) the algorithm the restore image distortion in SE-EPI diffusion weighted images (e) statistical analysis for correlating MR image information, both volumetric and diffusion measurements of subjects and their cognitive status.

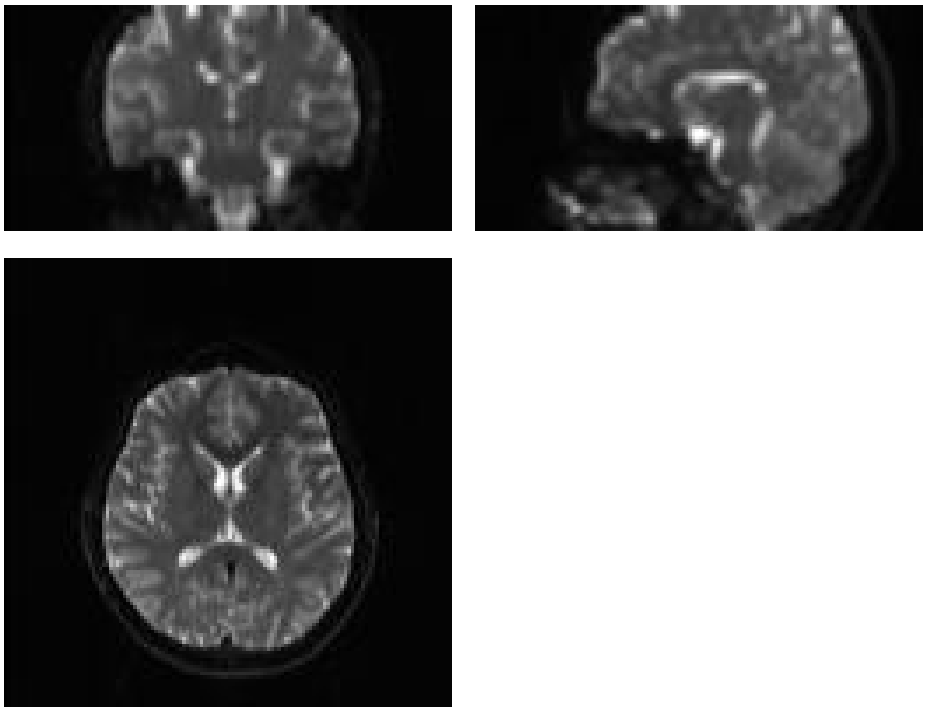

Fig. (1) T2* weighted echo planar images

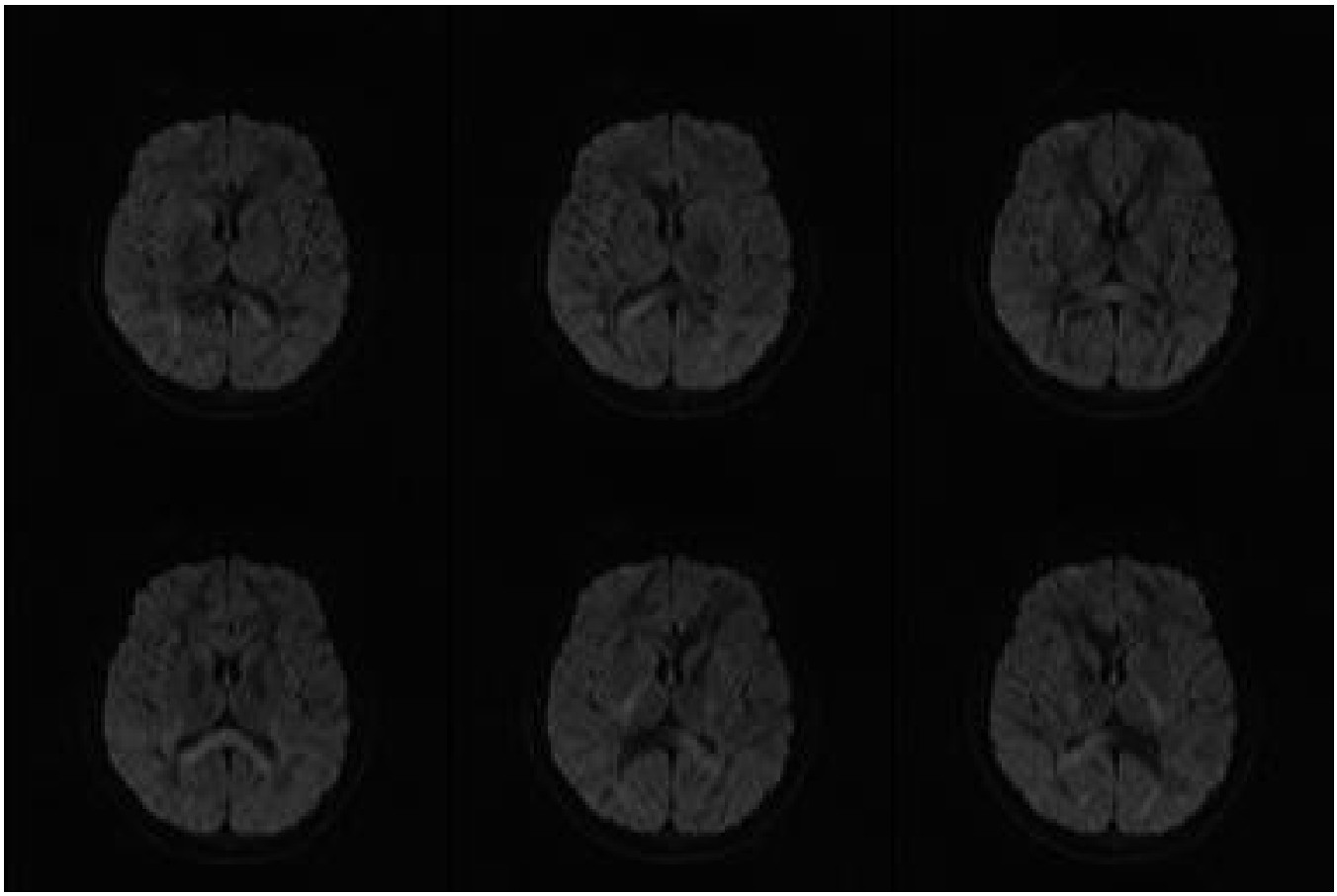

Fig. (2) Echo planar images with diffusion weighting in 6 different directions

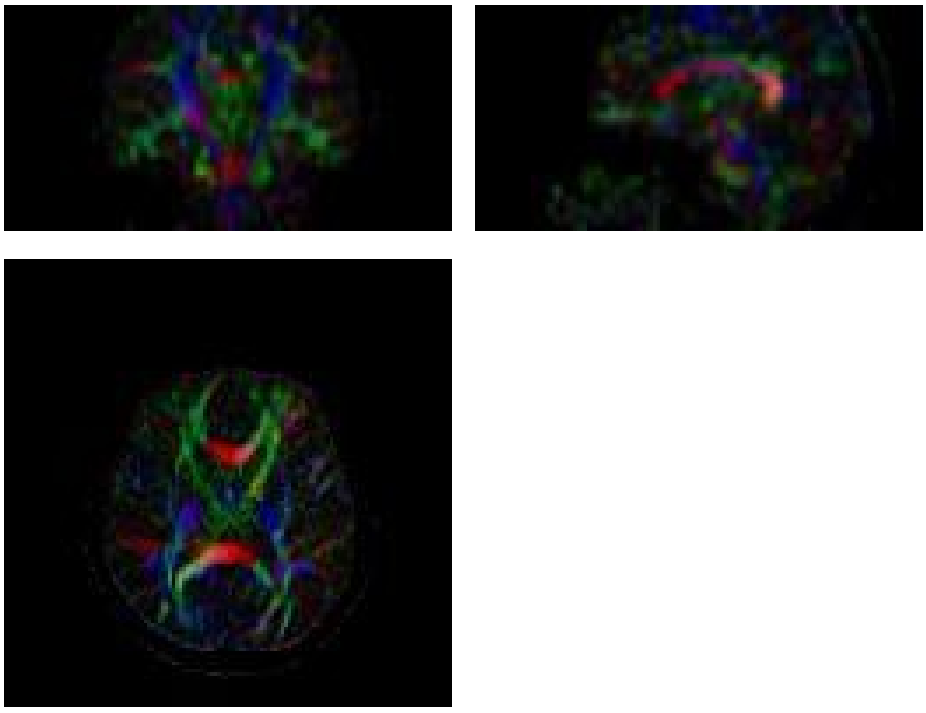

Fig. (3) Color-coded FA maps calculated from diffusion-weighted images

The items to be done in the second year in this study are as follows, (a) an image database with serial MR images follow-up every six months for AD related researches; (b) data analysis protocols for compute brain

atrophy, which include image realignment, nonlinear registration, and mapping of color overlay to baseline anatomic image; (c) calculation of changes in structure integrity of white matter tracts by registering serial diffusion measurements; (d) statistical analysis for correlating serial MR information, both volume and diffusion measurements of subjects and their cognitive status.

The items to be done in this study are as follows, (a) a completed image database built from 3 year longitudinal study for AD related researches, which includes subjects' detailed neuropsychologic assessments and their corresponding high resolution T1 weighted brain volume images and diffusion tensor images every six months; (b) imaging findings correlated with the conversion of MCI to AD; (c) white matter tractographic models for early detection of AD.

The contributions of conducting this project includes, (a) establishing an preliminary image model of progression of AD from the image database; (b) improving diagnosis of AD by advanced MR imaging.

The contributions of conducting this project includes, (a) establishing a more sophisticated image model of progression of AD from the image database with follow-up every six months; (b) detection of AD in early stage to initiate appropriate therapy and delay functional and cognitive losses; (c) correlating the results of image analysis with other research findings, such as evidences in molecular genetics, pathological progression, and treatment efficacy.

The contributions of conducting this project includes, (a) establishing an image model of progression of AD from the image database; (b) detection of AD in early stage to initiate appropriate therapy and delay functional and cognitive losses; (c) correlating the results of image analysis with other research findings, such as evidences in molecular genetics, pathological progression, and treatment efficacy.

The research team will obtain the following training by working in this research, (a) to understand the tools for neuropsychologic assessments; (b) to be familiar with the brain anatomy in MR images; (c) to develop the programming skills for ROI analysis and image segmentation; (d) to understand the theory of diffusion measurement in MR techniques, and corresponding post processing; (e) to analyze data with statistical correlation.

The research team will obtain the following training by working in this research, (a) to develop the programming skills for image registration for serial MR images; (b) to analyze data obtained from longitudinal study with statistical correlation in time series.

The research team will obtain the following training by working in this research, (a) to understand the tools for neuropsychologic assessments; (b) to be familiar with the brain anatomy in MR images; (c) to develop the programming skills for ROI analysis and image segmentation; (d) to analyze data with statistical correlation.

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