

Analysis of Morphological Brain Change of Alzheimer Disease (AD) Patients

Md. Shafiu Islam (Corresponding author)

Dept. of Applied Physics, Electronics and Communication Engineering
University of Dhaka, Bangladesh
Tel: 880-167-317-8070 E-mail: shafiu.ece@gmail.com

Saadia Binte Alam

Lecturer, International University of Business Agriculture and Technology
Dhaka, Bangladesh
Tel: 880-173-129-3340 E-mail: saadiabinte@yahoo.com

Rabeya Ferdousy

Dept. of Applied Physics, Electronics and Communication Engineering
University of Dhaka, Bangladesh
Tel: 880-171-745-9402 E-mail: ferdousyr@yahoo.com

Md. Enamul Hoque Chowdhury

Lecturer, Dept. of Applied Physics, Electronics and Communication Engineering
University of Dhaka, Bangladesh
Tel: 880-171-528-7542 E-mail: enamul@univdhaka.edu

Abstract

A growing body of evidence suggests that a preclinical phase of Alzheimer's disease (AD) exists several years or more prior to the overt manifestation of clinical symptoms and is characterized by subtle neuropsychological and brain changes. Identification of individuals prior to the development of significant clinical symptoms is imperative in order to have the greatest treatment impact by maintaining cognitive abilities and preserving quality of life. Functional magnetic resonance imaging (fMRI) offers considerable promise as a non-invasive tool for detecting morphological brain changes in Alzheimer disease affected patients. In fact, evidence to date indicates that functional brain decline precedes structural decline in preclinical samples. Therefore, fMRI may offer the unique ability to capture the dynamic state of change in the degenerating brain. This analysis examines morphological change in brain structure in those at risk for AD as well as in early AD. fMRI data analysis and findings is done on at-risk groups by collecting data from fMRI data centre which is gathered according to the virtue of genetic susceptibility or mild cognitive decline followed by an appraisal of the methodological issues concerning the diagnostic usefulness of fMRI in early AD. A total number of 28 subjects data, including 16 young Subjects data (18 and 30 year's of age) and 12 Alzheimer disease affected subjects data (65 and 92 year's of age) from fMRI data centre (www.fmridc.org) were analyzed in this paper. The analysis result shows that the cortex, hippocampus, and ventricle area of the Alzheimer diseased patients have shrunk dramatically than the normal subjects and other changes of brain are distinguishable. A discussion of data analyzing procedure has been given that will improve the ability to reliably detect early brain changes and will help for early identification of Alzheimer (AD) disease and to cure the disease.

Keywords: fMRI, Alzheimer disease (AD), FEAT, SIENA, BET, FLIRT, GLM and FWHM

1. Introduction

Senile dementia, which slowly destroys memory and thinking skills, and eventually even the ability to carry out the simplest tasks due to the toxic effects of a number of abnormal ("pathological") changes that occur in the brain and cause nerve cells in the brain die was renamed as Alzheimer's disease after Dr. Alois Alzheimer in

1906, who noticed changes in the brain tissue of a woman who had died of an unusual mental illness. After studying the patient's brain tissue in the microscope, Dr. Alzheimer observed the "plaques" and "tangles" which are now accepted as the hallmarks of the disease. As more and more plaques and tangles form in particular brain areas, healthy neurons begin to work less efficiently. Then, they lose their ability to function and communicate with each other, and eventually they die. This damaging process spreads to a nearby structure, called the hippocampus, which is essential in forming memories. As the death of neurons increases, affected brain regions begin to shrink. By the final stage of Alzheimer's, damage is widespread and brain tissue has shrunk significantly. Functional MRI (fMRI) reveal how well cells in various brain regions are actively using the sugar or oxygen brought by the brain's blood supply, functions of which significantly reduce in Alzheimer's disease. In this paper we have analyzed the fMRI data of a group of people to find out the affected areas of the brain so that we can identify the disease earlier and will be able to give better treatment to the patient to cure this deadly disease. After analyzing the fMRI data of a patient we can detect what kind of brain change have occurred inside the patient and detect whether it is Alzheimer diseases or not.

2. Subjects

From fMRI data centre we know that all subjects are right-handed, non-smokers, and without any special brain disease and sign of hypertension or psychological symptoms such as depression. All subjects data were examined clinically by both neurologists and psychologists and the criteria were also checked by interviewing subjects or their relatives by fMRI data centre. Here 18 and 30 years subjects are healthy subjects and 65 and 92 years subjects are affected by Alzheimer's disease. According to this clinical test, all Alzheimer's patients had GDS score of 6 or 7 and all healthy aging subjects had GDS of 1. It's worth mentioning that after processing among these 28 subjects' data finally four processed data of different aged subjects was used to show the difference of brain damaged portion between healthy subjects and Alzheimer disease patients.

3. MR Acquisition

All imaging was performed using a Siemens 1.5 Tesla Vision scanner (Erlangen, Germany). Cushions and a thermoplastic mask were used during scanning to reduce head movement. A scout image ($T_R = 15$ ms, $T_E = 6$ ms, flip angle = 30° , $2.34 \times 1.17 \times 8$ mm resolution) was acquired first in order to center the field of view on the brain. Four T1-weighted images (Mugler and Brookeman, 1991) scans ($T_R = 9.7$ ms, $T_E = 4$ ms, flip angle = 10° , $T_I = 20$ ms, $T_D = 200$ ms, $1 \times 1 \times 1.25$ mm resolution) were acquired in each subject by the fMRI data centre. Inter- and intra-scan motion correction and averaging were accomplished off-line.

4. Methodology

Normalized Whole Brain Volume was computed for each image session using a validated set of imaging tools from the FMRIB Software Library (Version 4.1.5, FSL, www.fmrib.ox.ac.uk/fsl) by Department of Clinical Neurology, University of Oxford. The following measurement procedures were conducted using the analyzing software. Images were displayed on computer and each given data was analyzed by different tools like BET, FLIRT, FEAT and SIENA by the software. Region-of-interest (ROI) was analyzed using the software between different ages of patients. SIENA (Structural image analysis evaluation with normalized atrophy) tool of the FSL software was used to analyze the data from fMRI data centre of different aged subjects to visualize how much there brain is affected due to Alzheimer disease and the differences between brain structures of different subjects according to their age also showed. Briefly, the images were pre-processed and skull-stripped using Brain Extraction Tool (BET). The skull-stripped images were then processed using FMRIB'S linear image registration tool (FLIRT) to get better output image from all subjects of specific age. The affected area of subjects of different ages are then showed using FMRIB'S expert analysis tool (FEAT). The theory and algorithm of voxel-based morphometry have been well documented. The acquired MR images were reformatted to gapless, 2.3-mm-thick transaxial images. Spatial normalization fitted each individual brain to a standard template brain in 3D space, to correct for differences in brain size and shape and to facilitate inter subject averaging. The gray matter images were smoothed with a 12-mm, full-width half-maximum non-gaussian kernel to use the partial volume effect to create a spectrum of gray matter intensities. The gray matter intensities are equivalent to the weighted average of gray voxels located in the volume fixed by the smoothing kernel; therefore, regional intensities can be taken as equivalent to gray matter volumes. The significance threshold for between-group differences was set at $P < 0.05$ (corrected for multiple comparisons across voxels), using the threshold-free cluster-enhancement option in the "randomize" permutation-testing tool in FSL. Image processing prior to regional analysis included several image registration steps ultimately resulting in registered structural data resampled to 1 mm³ voxels in the atlas space of Talairach and Tournoux. The following describes the image registration steps carried out for each individual. First, a 12-parameter affine atlas transform was computed.

Results from our laboratory indicate that atlas normalization, when using this young–old target atlas, is equivalent to normalization based on intracranial volume ($r = 0.44$) and is minimally biased. For each participant, the remaining images were registered to the first (allowing xyz stretch). Atlas transforms for all images were computed by transform composition (matrix multiplication). Each participant's averaged; atlas-transformed image was then produced using a single interpolation per scan. Intensity inhomogeneity was corrected using an algorithm minimizing intensity variation within continuous regions with the bias field modeled as a general second order polynomial in x, y, z . The preprocessing consisted of five stages: 1) spatial smoothing using a Gaussian kernel of FWHM of 5mm, 2) high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma = 100$ s), 3) slice-timing correction using Fourier-space time-series phase-shifting, 4) head motion correction using MCFLIRT (Motion Correction using FMRIB's Linear Image Registration Tool), 5) Standard analysis and brain extraction to remove non brain tissues using Brain Extraction Tool (BET, Version 1.1). The block diagram of the data analysis is shown in fig 1.1.

5. Group analysis between 18, 30, 65 and 92 year subjects

Brain extraction tool (BET) segments brain from non-brain and it deforms mesh model to fit brain surface also models skull & scalp surfaces. FMRIB's linear image registration tool (FLIRT) is used in inter- and intra-modal linear registration between-subjects and robust through use of multi-scale search & minimization adapted for MCFLIRT FMRI motion correction. FLIRT (FMRIB's Linear Image Registration Tool) do Linear/affine registration in 2D & 3D (various DOF) form and Uses all voxel intensities, not landmarks, robust to initial miss-alignment, choice interpolation methods and Configurable end-slice extrapolation. FLIRT provides a trade-off between speed and robustness. After doing BET and FLIRT between 18, 30, 65 and 92 year subjects, image processed output shown in fig 1.2, fig 1.3, fig 1.4, fig 1.5.

Now FEAT (FMRIB's expert analysis tool) is a software tool for high quality model-based FMRI data analysis, with an easy-to-use graphical user interface (GUI). FEAT is a part of FSL (FMRIB's Software Library). FEAT automates as many of the analysis decisions as possible, and allows easy (though still robust, efficient and valid) analysis of simple experiments whilst giving enough flexibility to also allow sophisticated analysis of the most complex experiments. It produces a web page analysis report, including color activation images and time-course plots of data vs. model. The data modeling which FEAT uses is based on general linear modeling (GLM), otherwise known as multiple regressions. It allows us to describe the experimental design; In FEAT, the GLM method used on first-level (time-series) data is known as FILM (FMRIB's Improved Linear Model). FILM uses a robust and accurate nonparametric estimation of time series autocorrelation to prewritten each voxel's time series; this gives improved estimation efficiency compared with methods that do not pre-whiten. FEAT saves many images to file - various filtered data, statistical output and color rendered output images - into a separate FEAT output directory for each session.

FEAT can also carry out the registration of the low resolution functional images to a high resolution scan, and registration of the high resolution scan to a standard (e.g. MNI152) image. By using this FEAT 5.0, FMRIB's analysis tool we tried to find out the affected area of 92 and 65 year old Alzheimer disease patient which is given in fig. 1.6 and fig. 1.7. SIENA (Structural image evaluation with normalized atrophy) is a package for both single-time-point ("cross-sectional") and two-time-point ("longitudinal") analysis of brain change, in particular, the estimation of atrophy (volumetric loss of brain tissue). SIENA estimates percentage brain volume change (PBVC) between two input images, at different points in time. It calls a series of FSL programs to strip the non-brain tissue from the two images, register the two brains (under the constraint that the skulls are used to hold the scaling constant during the registration) and analyze the brain change between the two time points. It is also possible to project the voxelwise atrophy measures into standard space in a way that allows for multi-subject voxelwise statistical testing.

By using this SIENA analysis tool from FSL we tried to distinguish between 18, 30, 65 and 92 year old Alzheimer disease (AD) patient. After image processing the output result is shown in fig 1.8, fig 1.9 and fig 1.10. Using this analysis tool we can also distinguish between the ventricle change of 18 year subject and 92 year old Alzheimer disease patient and between 65 year subject and 92 year old Alzheimer disease patient. After image processing the output is shown in fig 1.11. From the 3D image we can also see how much the structure of brain changes between different subjects due to Alzheimer disease which is shown in fig 1.12, fig 1.13, fig 1.14 and fig 1.15.

6. Result

Our study indicates that morphologic changes associated with normal aging clearly differ from those associated with AD. Patients with AD had decreased gray matter volumes in the medial temporal structure, hippocampus,

entorhinal cortex, and parahippocampal gyrus, which are believed to constitute the long-term-memory system. This has been observed that nerve cells die and disappear from the part of the brain that shrunk. This process, which first begins in the part of the brain that deals with thinking and memory, is progressive, eventually affecting all parts of the brain, which consequently shrinks as a whole. The shrinkage is most marked, however, in the thinking and memory regions, and this is very readily seen by brain imaging.

In our group analysis study between 18 and 92 year subjects and we have seen from fig. 1.8 that the cortex cerebellum area shrivels up more for 92 year aged AD patient than 18 year subject. This damaging area greatly involved in thinking, planning and remembering. From fig. 1.8 we can also see that the shrink begins especially severe in the hippocampus area which plays a key role in formation of new memories. From fig 1.11 we can also see that the ventricles (fluid filled spaces within the brain) for 92 year old AD patient have grown larger than 18 year old subject due to damage in nerve cells affected by Alzheimer disease. For 92 and 65 year's old Alzheimer disease patient the region of corpus callosum (CC) is shattered and become almost indistinguishable due to dead nerve cells which can also be easily seen from fig. 1.6 and fig. 1.7. From fig 1.12, 1.13, 1.14 and 1.15 the 3D image view of 18, 30, 65 and 92 year subject we can see that the size of brain of 92 year old AD patient is shrinking respect to 18 and 30 year old subject due damaging of brain nerve cells day by day. Almost similar changes we have seen for Group analysis between 30 and 92 years old subject and between 65 and 92 years old Alzheimer disease patient. So due to Alzheimer disease the cortex, corpus callosum, hippocampus and ventricles area of the brain is damaged, forgetfulness gradually increases, and in the later stages it becomes ultimately fatal, and death usually occurs within seven to 10 years after diagnosis.

7. Conclusions

Similar to all renowned research work, after analyzing the data from fMRI data centre of different subjects we have seen the cortex and hippocampus region of the brain have reduced significantly due to AD and also the ventricles have grown larger. The volume of the brain of an AD patient also becomes smaller than a normal subject. All of these affected areas are polymodal and association cortices of the limbic system, believed to be related to cognitive processes that include attention, working memory, and the control of behavior. Damage to these areas, therefore, leads to cognitive changes observed in the elderly AD patients. When aged people were tested with neuropsychological tests, cortex and hippocampus region seemed to be a primary component of their cognitive impairments. The results of this study provide some support for these behavioral data. Several postmortem and neuro imaging studies have suggested that hippocampus, ventricles and gyrus should be the most severely affected, whereas primary visual and somatosensory cortices might be more resistant to the influence of this disease. Our study indicates an AD related decline in hippocampus, gyrus, corpus callosum and ventricles. Some neuropathology studies also suggested that the insular cortex atrophy involved in AD show substantial reduction in hippocampus volume, In contrast, AD effects include significant reductions in callosal volume with an anterior-to-posterior gradient. Moreover, anterior (frontal) callosal differences are not accelerated by early-stage AD, suggesting they are unlikely to contribute to initial stages of AD. Fibers and loss of small diameter myelinated fibers in subcortical white matter with advancing age increases. Previous reports have noted atrophy of posterior callosal regions in early-stages of AD that may be similar in magnitude to medial temporal atrophy. It is possible that neocortical degeneration sufficient to result in callosal effects may be present in later stages of AD.

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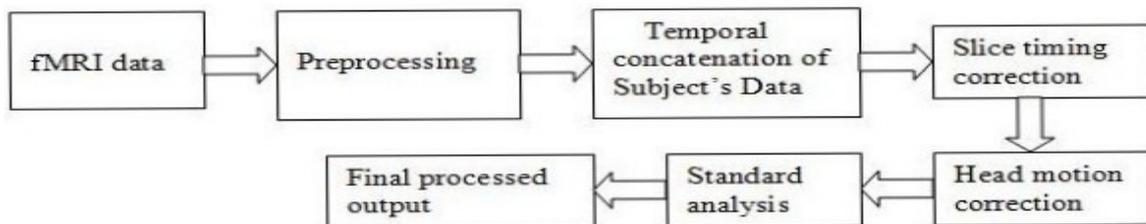


Figure 1.1. Processing steps of fMRI data

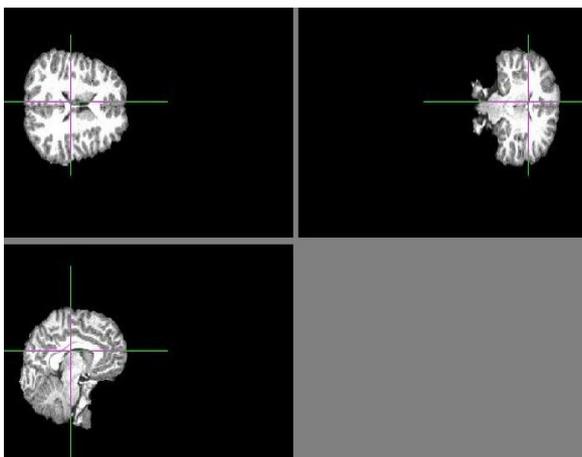


Figure 1.2. 18 year old subject

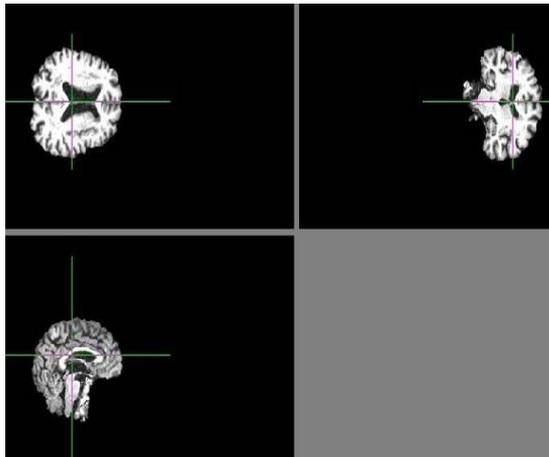


Figure 1.3. 92 year old subject

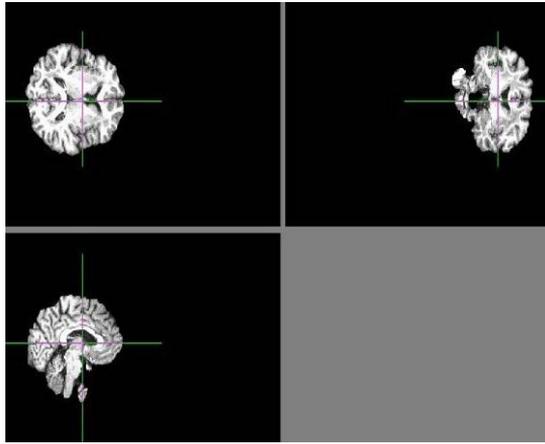


Figure 1.4. 30 year old subject

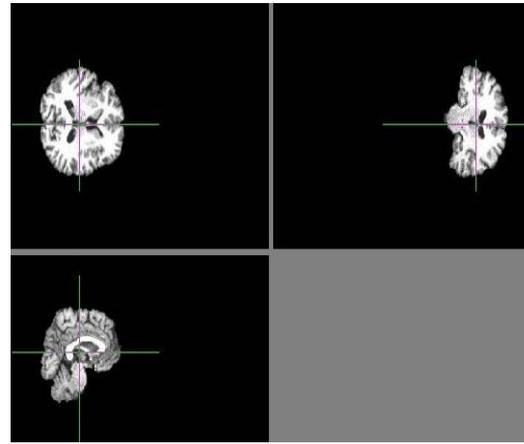


Figure 1.5. 65 year old subject

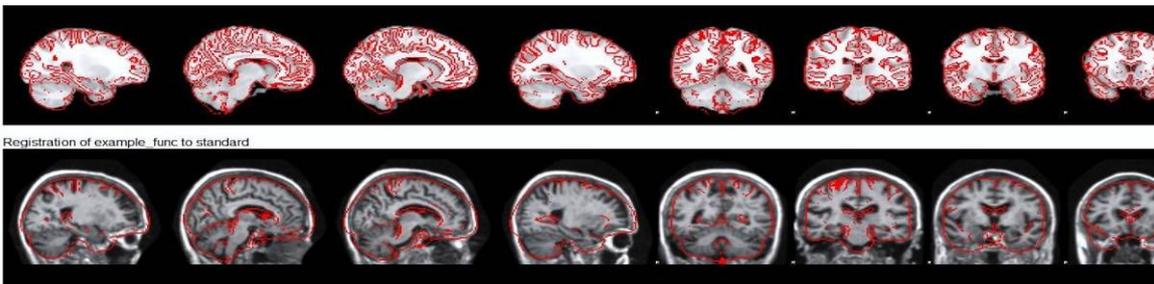


Figure 1.6. Brain affected area of a 92 year old Alzheimer disease patient

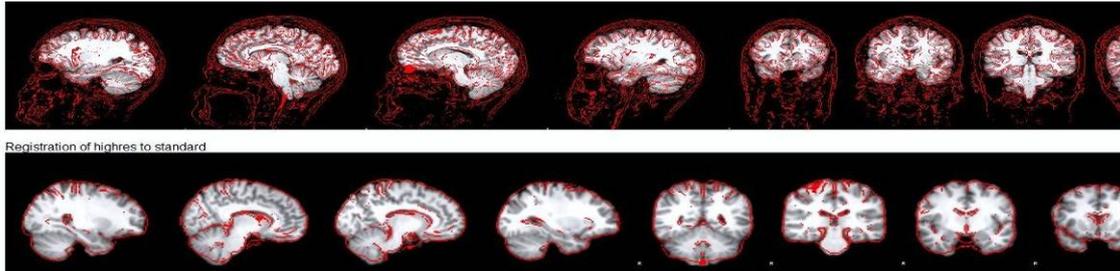


Figure 1.7. Brain affected area of a 65 year old Alzheimer disease patient

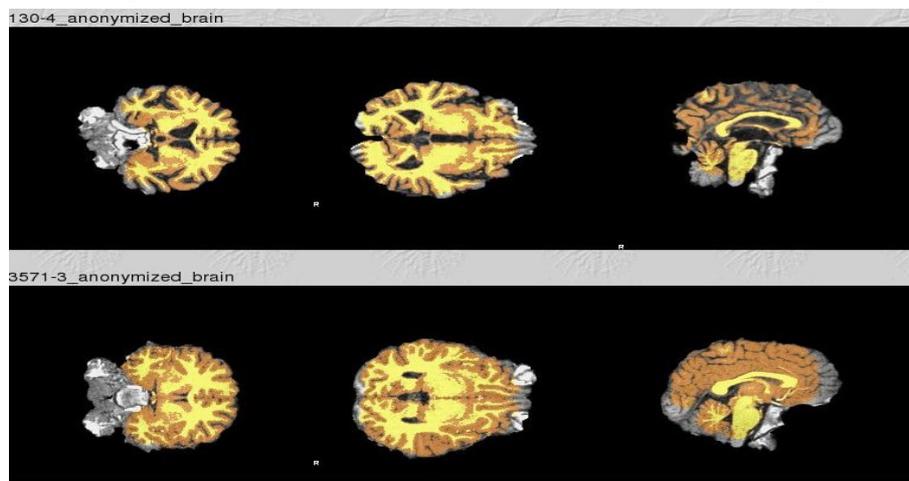


Figure 1.8. Distinguishing between 18 year subject and 92 year Alzheimer old disease patient. Upper image represents 92 year Alzheimer disease patient and lower image represents 18 year subject

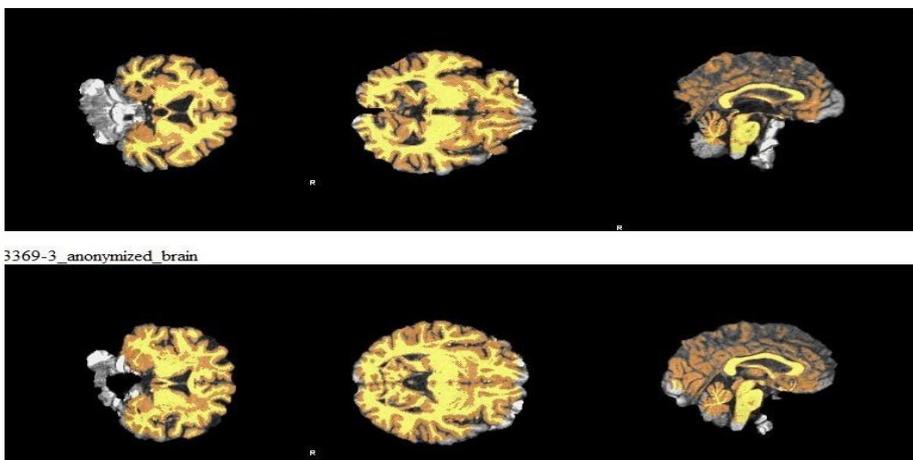


Figure 1.9. Distinguishing between 30 year subject and 92 year Alzheimer disease patient. Upper image represents 92 year Alzheimer disease patient and lower image represents 30 year subject

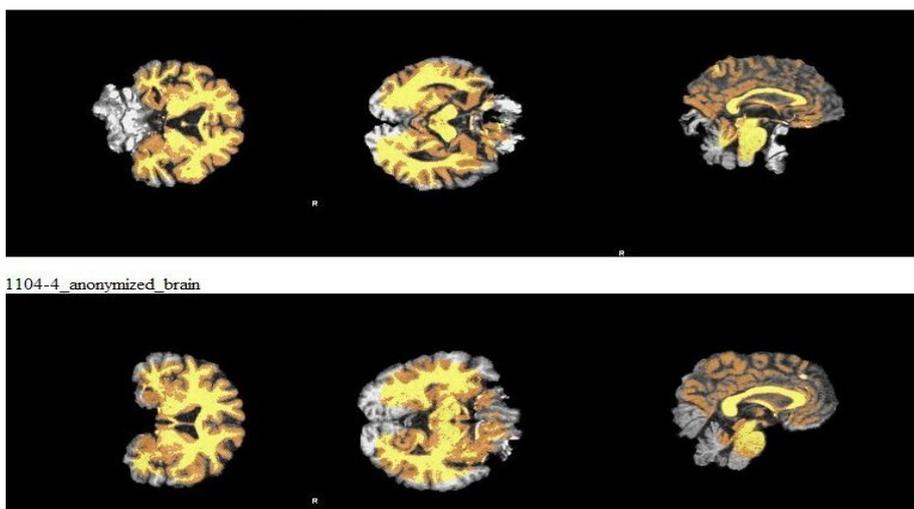


Figure 1.10. Distinguishing between 65 year subject and 92 year Alzheimer disease patient. Upper image represents 92 year Alzheimer disease patient and lower image represents 65 year subject

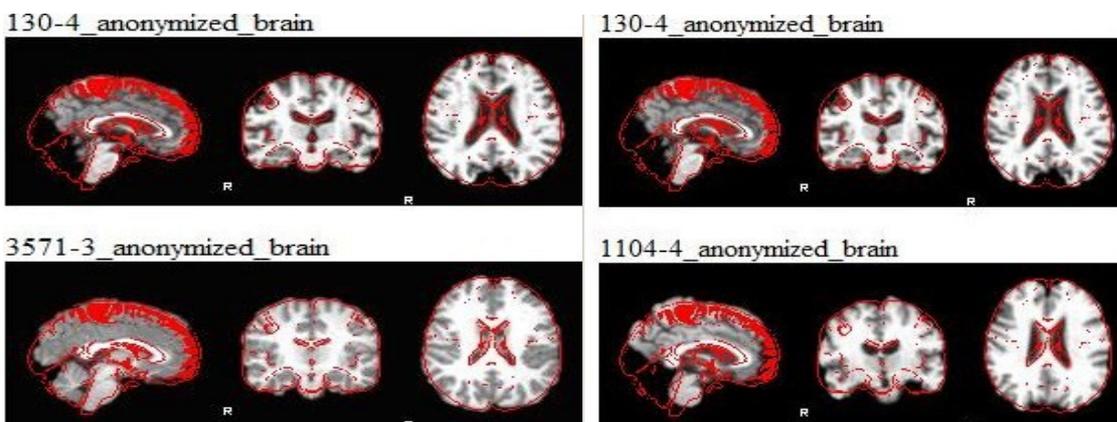


Figure 1.11. Distinguishing between ventricles of 18 year subject and 92 year Alzheimer disease patient and between 65 year subject and 92 year old Alzheimer disease patient. Upper image represents 92 year Alzheimer disease patient and lower image represents 18 and 65 year subject

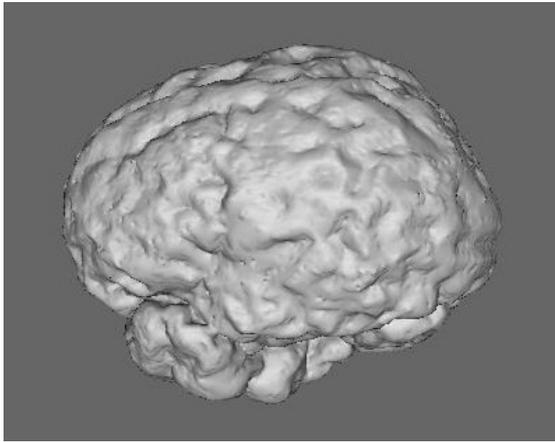


Figure 1.12. 3D brain structure of 18 year subject

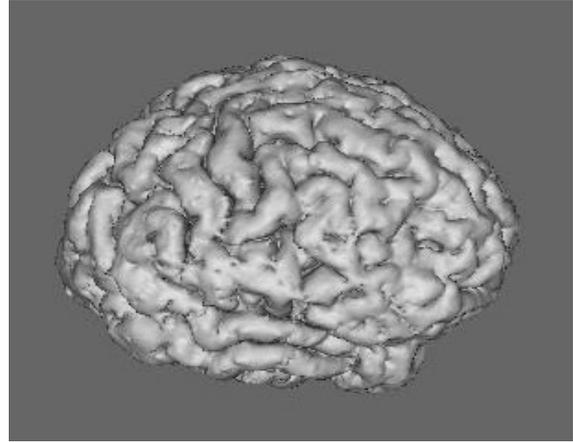


Figure 1.13. 3D brain structure of 92 year AD patient

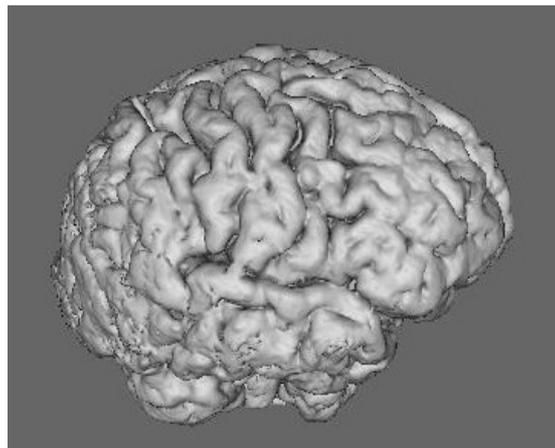


Figure 1.14. 3D brain structure of 30 year subject

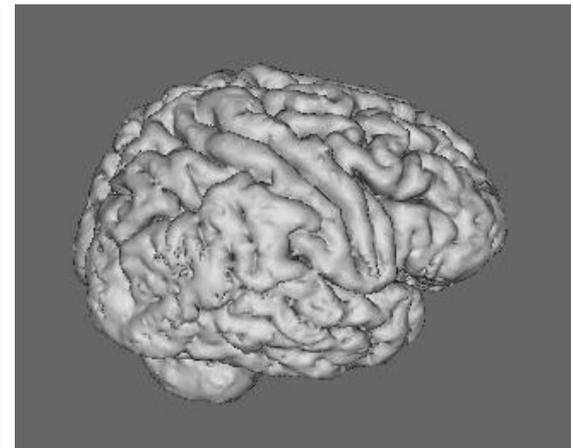


Figure 1.15. 3D brain structure of 65 year subject