



Faculty of medicine

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# **Diffusion Tensor Imaging of white matter degeneration in Alzheimer disease**

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for the Master degree in Diagnostic Radiology

BY

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# Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, accounting for 60-70% of all demented cases. (Fratiglioni et al. 2007). It is a neuro-pathological diagnosis determined by presence of neurofibrillary tangles and senile plaques in the brain of patients with dementia. The disease frequently starts with memory impairment, but is invariably followed by a progressive global cognitive impairment. (Harvey et al. 1999).

Alzheimer's disease including a review of factors that increase or reduce its risk. (Mayeux & Stern, 2012). The major risk factor for Alzheimer disease is age, with prevalence doubling every 5 years after the age of 65 (Brookmeyer et al. 1998). Vascular risk factors such as hypertension, elevated cholesterol levels, Diabetes, obesity and Apo-E4 gene.

The prevalence of Alzheimer disease in 2002 was estimated to be 2.3 million individuals over age of 70, based on a national population-based sample. (Plassman et al. 2007). By Looking to the future, the number of Americans surviving to 80s, 90s and beyond is expected to grow dramatically due to medical advances as well as social and environmental conditions. (Ortman et al. 2014). So number of new cases and existing cases of Alzheimer's disease grows rapidly. In 2010, there were estimated 454,000 new cases of Alzheimer's disease. By 2025, the number of people age 65 and older with Alzheimer's disease is estimated to reach 7.1 million (almost 40% increase from the 5.2 million age 65 and older affected in 2016). By 2050, the number of people age 65 and older with Alzheimer's disease may nearly triple from 5.2 million to a projected 13.8 million. (Hebert et al. 2013). Alzheimer's disease is becoming a more common cause of death. As severe dementia causes complications such as immobility, swallowing disorders and malnutrition that significantly increase the risk of other serious conditions that can cause death. One such condition is pneumonia, which is the most commonly identified cause of death among elderly people with Alzheimer's disease. (Brunnstorm HR, England EM. 2009). Between 2000 and 2013, deaths attributed to Alzheimer's disease increased 71% while those attributed to other causes of death such as heart disease decreased 14%, stroke decreased by 23%. Many researchers believe that early detection of Alzheimer's disease will be key to preventing, slowing, stopping the progression of the disease and preserve brain function. Future treatments (called "disease-modifying" treatments) will be most effective when administered early in the disease; either at the mild cognitive impairment (MCI) stage or during the proposed preclinical stage especially in cases with a lower burden of Amyloid and Hyperphosphorylated tau and can attenuate the negative effects of secondary events caused by deposit of those toxic products in tissues. Biomarker tests will be essential to identify which individuals are in these early stages and should receive disease-modifying treatment when it becomes available. They also will be critical for monitoring the effects of treatment. (Albert et al. 2011). Brain changes associated with Alzheimer's disease are variable; a healthy adult brain has about 100 billion neurons, each with long, branching extensions. These extensions enable individual neurons to form connections with other neurons. At such connections, called synapses. The brain contains about 100 trillion synapses. They allow signals to travel rapidly through the brain's neuronal circuits, creating

the cellular basis of memories, thoughts, sensations, emotions, movements and skills. The accumulation of the protein beta-amyloid (called beta-amyloid plaques) outside neurons and the accumulation of an abnormal form of the protein tau (called tau tangles) inside neurons are two of several brain changes believed to contribute to the damage and destruction of neurons that result in memory loss and other symptoms of Alzheimer's. As brain changes advance, information transfer at synapses begins to fail, the number of synapses declines, and neurons eventually die. The accumulation of beta-amyloid is believed to interfere with the neuron-to-neuron communication at synapses and to contribute to cell death. Tau tangles block the transport of nutrients and other essential molecules inside neurons and are also believed to contribute to cell death. The brains of people with advanced Alzheimer's disease show inflammation, dramatic shrinkage from cell loss, and widespread debris from dead and dying neurons. The brain changes associated with Alzheimer's may begin 20 or more years before symptoms appear. When the initial changes occur, the brain compensates for them, enabling individuals to continue to function normally. As neuronal damage increases, the brain can no longer compensate for the changes and individuals show subtle cognitive decline. Later, neuronal damage is so significant that individuals show obvious cognitive decline, including symptoms such as memory loss or confusion to time or place. Later still, basic bodily functions such as swallowing are impaired. (Bateman et al. 2012).

Diagnosis of Alzheimer's typically involves physical and neurological exams, as medical history and mental status evaluation, laboratory investigations and it involves brain imaging (such as MRI) which could identify other causes of problems such as stroke, tumor or head trauma. By physical and neurological examination, Alzheimer's disease characterized by gradual onset and progressive decline in cognition with sparing of motor and sensory function until later stages; the average course of Alzheimer's disease is approximately a decade, with a range of 3 to 20 years duration from diagnosis to death. Memory impairment is present in the earliest stages of the disease; patients have difficulty learning new information and retaining it for more than few minutes. As the disease advances, the ability to learn increasingly compromised, more distant memories are lost. Other cognitive losses include aphasia, apraxia, disorientation and impaired judgment. Cognitive impairment affects daily life; patients have difficulty planning meals, managing finances or medication, using telephone, driving. Many capacities may remain intact until later stages including performance of self-care activities of daily living as eating, bathing. Patients evidence personality alteration, irritability, anxiety, depression. Delusion, hallucination and aggression. (Stern et al.1994).Laboratory Evaluation includes Biochemical markers as measurement of CSF including Tau protein, amyloid beta peptides or neural thread protein and measurement of urinary biomarkers including neural thread protein. Also genotyping testing including Apo lipoprotein E epsilon 4 allele presenilin genes, amyloid precursor gene or TREM2.APOE gene provides a blueprint for a protein that transports cholesterol in the blood stream. Everyone inherits one of three forms of APOE gene – e2, e3, e4. The e3 form is the most common; the e2 form is the least common. The e4 form is more common than e2 form. People with one or two copies of e4 are at higher risk of develop Alzheimer's disease than individuals who don't have copy of e4. (Raber et al.2004).

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Most of the past imaging studies concentrated on the damage of grey matter based on voxel-based morphometry (VBM), some studies point to regional grey matter atrophy mainly medial and lateral areas as the sites of highest atrophy while parieto-temporal areas, precuneus, post and ant cingulate gyri, thalamus, caudate nucleus and putamen show significant but lower grey matter loss. (Karas et al., 2004). Positron emission tomography (PET) studies have highlighted early glucose hypometabolism in posterior associative cortical areas, especially in the posterior cingulate cortex and subsequently in dorsolateral and medial frontal areas and preisylvian and insular cortex. (Morbelli et al., 2012). Studies of cadaver brain revealed that white matter changes are strongly associated with Alzheimer's disease. It's found that the White matter had significant pathological changes including demyelination and loss of Axons, DNA breakage and lack of plasmalogen lipids in Alzheimer's disease at early stage. (Villain et al. 2008). Previous studies use Functional MRI to detect alteration in several white matter tracts in Alzheimer's disease particularly the corpus callosum, cingulum bundle, fornix and uncinate fasciculus. (Hempel et al. 1998). They found that AD associated microstructural white matter pathology is not homogeneously distributed, but it rather involves selectively brain white matter regions which are connected with the association cortices (corpus callosum and white matter of the temporal, frontal and parietal lobe) with a relative sparing of other white matter areas subserving motor (internal capsule) or visual (optic radiations). (Vermersch et al, 1996.)

As Diffusion tensor imaging (DTI) is an imaging technology based on magnetic resonance diffusion weighted imaging, which can make quantitative analysis of anisotropy of water molecules in different directions, so as to observe the microstructure of tissues non-invasively. So DTI can provide information of fiber orientation, the injury of fiber, and membrane permeability which cannot be obtained from conventional MRI. DTI enables mapping of WM microstructure changes in development, aging and neurological disorders, From the tensor, it's possible to derive the mean diffusivity (DM) and the fractional anisotropy (FA) which is the most robust measures of anisotropy which measure the degree of deviation from isotropic diffusion. (Pierpaoli et al. 1996). More recently, an additional DT-MRI derived index has been proposed (Pfefferbaum et al. 2000). This index measures the degree of similarity of orientation of neighboring voxels and its named inter-voxel coherency (C). So DTI has therefore become a powerful technique in the study of neurodegenerative diseases in recent years. So the aim of the present study to point to the alteration of several white matter tracts in Alzheimer's disease. In the present study, by DT-MRI (we will calculate D, FA) to investigate the extent of tissue damage of several brain white matter regions in patients with Alzheimer's disease. The ultimate goal of the study is to provide a complete picture of the distribution of microstructural white matter damage in Alzheimer's disease and to improve our understanding of their nature.

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## **Aim of the work:**

To study role of diffusion tensor imaging (DTI) to detect changes in white matter microstructure in patients with Alzheimer's disease.

## Patient and method

### Patient:

The study will be performed at the Radiodiagnosis department of Assiut University Hospital.

Selection of 20 patients clinically and laboratory diagnosed as Alzheimer disease and another 20 people matched healthy controls who have no complaints of cognitive problems.

### Inclusion criteria:

The inclusion criteria for the patients: (1) cognitive complaints with interference in complex occupational and social activities, (2) changes in cognition reported by the patient, informant or clinician, (3) absence of profound subcortical ischemic changes.

### Exclusion criteria:

To minimize the inclusion of patients with Alzheimer's disease and associated major ischemic vascular disorders.

The exclusion criteria were: (1) state of delirium; (2) stroke event within 2 weeks; (3) appearance of cortical and /cortico-subcortical non-lacunar territorial infarcts and watershed infarcts, hemorrhage, signs of normal pressure hydrocephalus, and specific causes of white matter lesions (e.g. multiple sclerosis, sarcoidosis, brain irradiation), (4) derangements in serology tests contributing to cognitive impairment (e.g. abnormal levels of free T4, cortisol, folic acid, vitamin B12, or rapid plasma reagin), and (5) severe hearing or visual impairment, (6) cases of severe dementia.

### Patient preparation

To acquire an optimal MRI examination, adequate patient preparation is as important as the optimization of the technique. 1) Psychological preparation of the patient including the scanner environment. 2) Confirmation of absence of any paramagnetic substance.

### Technique

Compared DTI findings among AD, MCI or elderly healthy controls. The main DTI measures used were FA, ADC and MD. Other measures were occasionally cited such as radial diffusivity and axial diffusivity. The most relevant encephalic regions assessed were temporal areas, parietal areas, frontal areas, posterior areas, and some integrative intra-cortical fiber tracts. Specific structures such as the corpus callosum, cingulate gyrus/ cingulate fiber tracts, uncinate fasciculus, inferior longitudinal fasciculus/superior

longitudinal fasciculus fiber pathways and hippocampus were studied. Other structures were cited as secondary including thalamus, basal ganglia, and internal capsule. The main DTI measures (FA and ADC) of the above mentioned encephalic structures showed compromised tissue integrity and marked changes in relevant fiber tracts, from very early AD stages. These findings were found to correlate with cognitive assessments, and also differentiated between normal ageing, AD.

### MRI acquisition

Brain MR Scans were obtained on a magnet operating at 1.5 T. On a single occasion, images using the following pulse sequences were obtained from all subjects without moving them from the scanner:(a) dual echo turbo spin echo (TSE) (TR=3300 ms, TE=16/98 ms, echo train length=5); (b) T1 weighted SE (TR=650 ms, TE=12 ms); (c) pulsed gradient spin echo (PGSE) echo planar pulse sequence (interecho spacing=0.8 ms, TE=123 ms), with diffusion gradients applied in eight non-collinear directions ,chosen to cover three dimensional space uniformly.<sup>26</sup> The duration and maximum amplitude of the diffusion gradients were respectively 25 ms and 21 mTm<sup>-1</sup>,giving a maximum b factor in each direction of 1044 s mm<sup>-2</sup>. To optimize the measurement of diffusion only two b factors were used<sup>27</sup> (b<sub>1</sub>≈0, b<sub>2</sub>=1044 s mm<sup>-2</sup>). Fat saturation was performed using a four radio frequency binomial pulse train to avoid chemical shift artifact. A birdcage head coil of ~300 mm diameter was used for signal transmission and reception. For the dual echo and T1 weighted sequences, 24 contiguous interleaved axial slices were acquired with 5 mm slice thickness, 256×256 matrix and 250×250 mm field of view. The slices were positioned to run parallel to a line that joins the most inferoanterior and inferoposterior parts of the corpus callosum. For the PGSE scans, 10 5 mm thick slices were acquired, with the same orientation of the dual echo scans, positioning the second last caudal slice to match exactly the central slices of the other image sets. This set of slices was chosen as these central slices are less affected by the distortions due to B<sub>0</sub> field inhomogeneity, which can affect image co-registration .Also, this set of slices allowed us to cover a relatively large portion of the cerebral hemispheres where white matter is highly represented. PGSE images had a 128×128 matrix and a 250×250 mm field of view.

### **Ethical consideration**

- The study of protocol will be submitted for ethical committee of the Faculty of medicine Assuit University for revision and approval.
- All subjects included in the study will be consented after detailed explanation of the nature of the study and its procedures.
- Privacy and confidentiality of the obtained data will be assured.
- There is no probability of risk or harm for the subjects enrolled in the study.
- Psychological preparation of the patient including the scanner environment.

- Confirmation of absence of paramagnetic substance.

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