Course Code: Ana 302

Course Title: Radiologic Anatomy

Group: 1

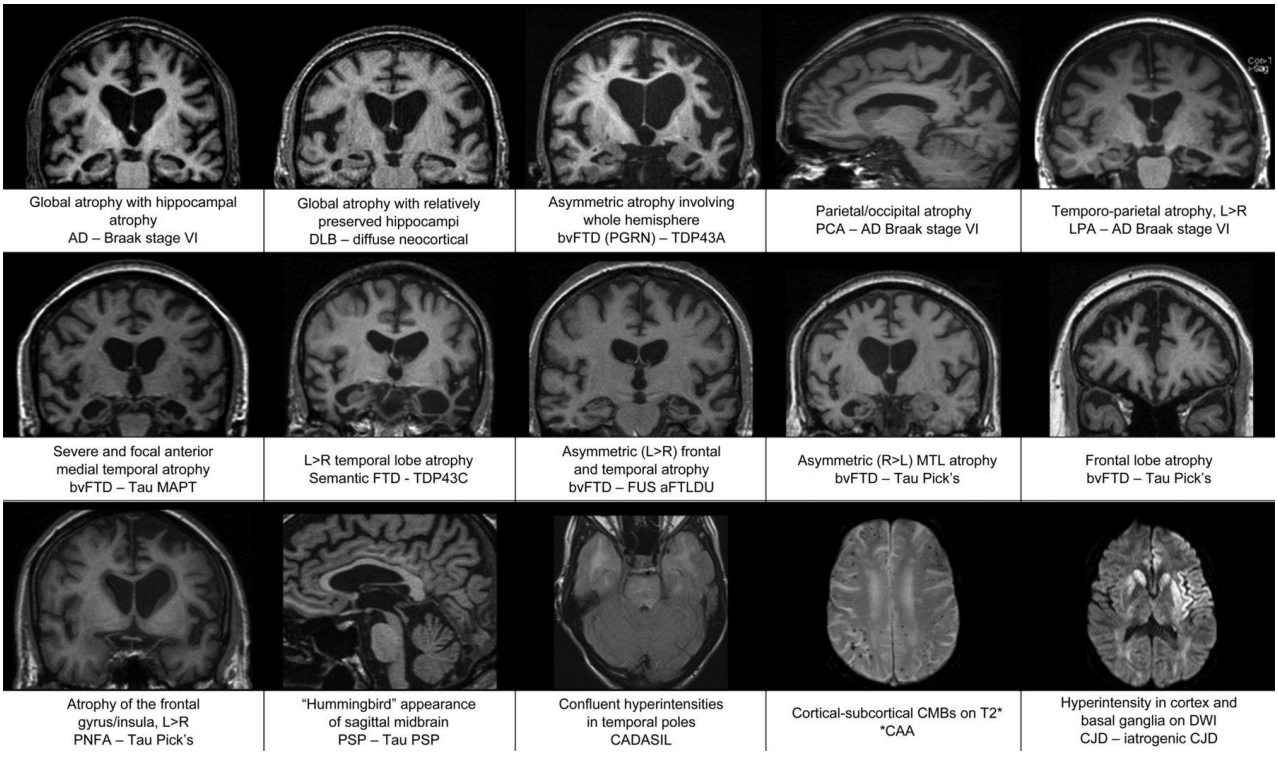
Topic: Application Of Imaging Techniques Towards Alzheimer's Disease

Lecturer: Dr ENYE, Linus Anderson

NAME	MATRIC NUMBER
GUWOR-NIKI Bolouere	17/MHS03/018
SALIU Halima	17/MHS01/294
FAKUNLE Bankole	18/MHS03/020
EJEH Hillary	17/MHS03/014
OBASI Kosisochukwu Cindy	17/MHS01/218
OSIBANJO Iyanuoluwa	17/MHS03/029

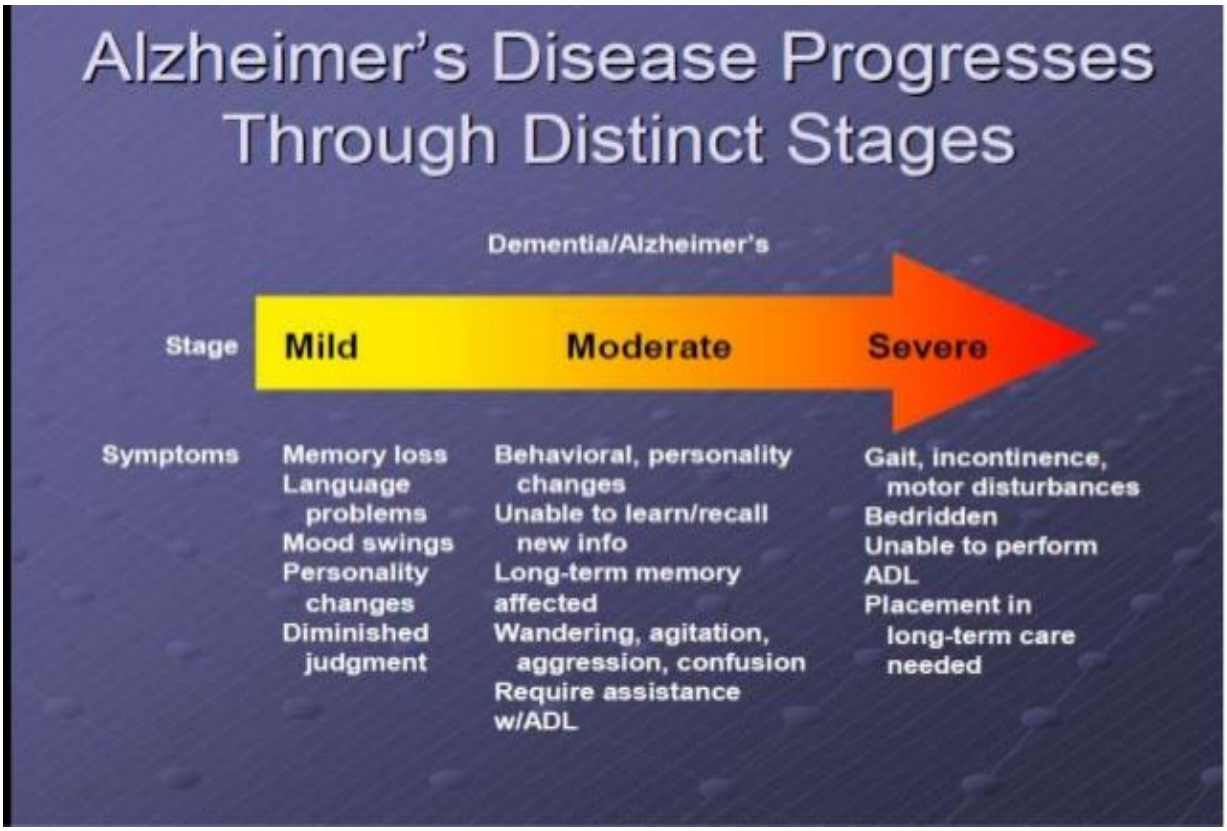
INTRODUCTION

Dementia is a syndrome characterized by disturbance of multiple brain functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation (WHO, 1992). Alzheimer disease is the most common form of dementia and possibly contributes to 60-70% of cases. Other types of dementias include vascular dementia, dementia with Lewy bodies, and a group of diseases that contribute to frontotemporal dementia. The boundaries between subtypes are indistinct and mixed forms often co-exist.



Brief Description of Alzheimer Disease

Alzheimer disease (AD) is characterized by a progressive decline in cognitive function. AD is substantially increased among people aged 65 years or more, 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. Disease often starts with mild symptoms and ends with severe brain damage. People with dementia lose their abilities at different rates. (Honjo *et al.*, 2012). The pathophysiology of AD is related to the injury and death of neurons, initiating in the hippocampus brain region that is involved with memory and learning, then atrophy affects the entire brain (Coleman *et al.*, 2013). Amyloid beta, also written Aβ, is a short peptide that is an abnormal proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. Amyloid beta monomers are soluble and contain short regions of beta sheet at sufficiently high concentration, they undergo a dramatic conformational change to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils. These fibrils deposit outside neurons in dense formations known as senile plaques or neuritic plaques, in less dense aggregates as diffuse plaques, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy or congophilic angiopathie. In Alzheimer disease abnormal aggregation of the tau protein, a microtubule-associated protein expressed in neurons is also observed. Tau protein acts to stabilize microtubules in the cell cytoskeleton. Like most microtubule-associated proteins, tau is normally regulated by phosphorylation. In AD patients, hyperphosphorylated tau P-tau accumulates as paired helical filaments that in turn aggregate into masses inside nerve cell bodies known as neurofibrillary tangles and as dystrophic neurites associated with amyloid plaques.



Importance of imaging as regards to Alzheimers disease.

Imaging has a major role to play in improving our understanding of this disease (or diseases). Uniquely, imaging is able to delineate in life the location within the brain of the effects of AD. Together with this topographical information imaging can quantify multiple different aspects of AD pathology and assess how they relate to each other and how they change over time. The clinical correlations of these changes and their relationships to other biomarkers and to prognosis can be studied. Ultimately, the role of imaging in improving our understanding of the biology of AD underpins all its applications and is a theme that runs through the following sections of this article.

Neuroimaging in Alzheimers disease

There has been a transformation in the part played by neuroimaging in Alzheimer disease (AD) research and practice in the last decades. Diagnostically, imaging has moved from a minor exclusionary role to a central position. In research, imaging is helping address many of the scientific questions outlined in 'providing insights into the effects of AD and its temporal and spatial evolution' (Selkow *et al*., 2011). Furthermore, imaging is an established tool in drug discovery, increasingly required in therapeutic trials as part of inclusion criteria, as a safety marker, and as an outcome measure. Concomitantly the potential of brain imaging has expanded rapidly with new modalities and novel ways of acquiring images and of analysing them. This article cannot be comprehensive. Instead, it addresses broad categories of structural, functional, and molecular imaging in AD. The specific modalities included are magnetic resonance imaging (MRI; both structural and functional) and positron emission tomography (PET; for assessment of both cerebral metabolism and amyloid). These modalities have different strengths and limitations and as a result have different and often complementary roles and scope.

Diagnosis.

Historically, imaging first computed tomography (CT) and then MRI was used only to exclude potentially surgically treatable causes of cognitive decline. Now its position in diagnosis also includes providing positive support for a clinical diagnosis of AD in symptomatic individuals by identifying characteristic patterns (signatures) of structural and functional cerebral alterations. We can now also visualize the specific molecular pathology of the disease amyloid deposits with amyloid imaging. Alongside this increasing specificity for AD, imaging also contributes to differential diagnosis in practice by identifying alternative and/or contributory pathologies.

Imaging is central to identifying vascular and non-AD degenerative pathologies and has helped in the recognition of the prevalence of mixed pathology in dementia.

However, brain imaging can help:

- Rule out other causes, such as hemorrhages, brain tumors or strokes
- Distinguish between different types of degenerative brain disease
- Establish a baseline about the degree of degeneration

The brain-imaging technologies most often used are:

- **Magnetic resonance imaging (MRI).** An MRI uses powerful radio waves and magnets to create a detailed view of your brain.
- **Computerized tomography (CT).** A CT scan uses X-rays to obtain cross-sectional images of your brain.
- **Positron emission tomography (PET).** A PET scan uses a radioactive substance known as a tracer to detect substances in the body. There are different types of PET scans. The most commonly used PET scan is a fluorodeoxyglucose (FDG) PET scan, which can identify brain regions with decreased glucose metabolism. The pattern of metabolism change can distinguish between different types of degenerative brain disease.

  PET scans have recently been developed that detect clusters of amyloid proteins (plaques), which are associated with Alzheimer's dementia, but this type of PET scan is typically used in the research setting.

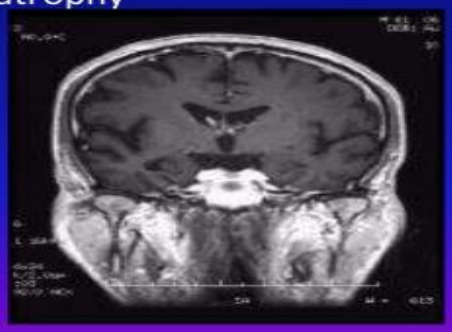
Magnetic resonance imaging (MRI).

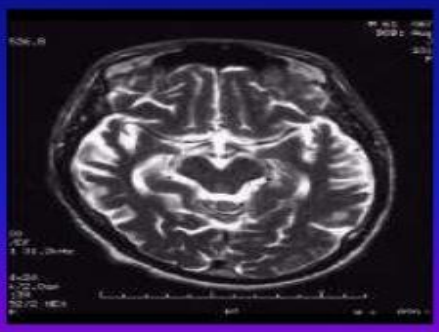
Basics of Structural MRI as Applied to AD

MRI utilizes the fact that protons have angular momentum which is polarized in a magnetic field. This means that a pulse of radiofrequency can alter the energy state of protons and, when the pulse is turned off, the protons will, on returning to their energy stage, emit a radiofrequency signal. By a combination of different gradients and pulses, “sequences” can be designed to be sensitive to different tissue characteristics. In broad terms structural MRI in AD can be divided into assessing atrophy (or volumes) and changes in tissue characteristics which cause signal alterations on certain sequences such as white matter hyperintensities on T2-weighted MRI as a result of vascular damage. A number of MR sequences that are sensitive to microstructural change (e.g., magnetization transfer or diffusion) have shown alterations in AD. These sequences are already important research tools; however, they have not yet found a place in routine clinical practice in AD and they will not be considered further here.

MRI

- Many studies have shown that cerebral atrophy is significantly greater in patients with Alzheimer disease than in persons without it. However, the variability of atrophy in the normal aging process makes it difficult to use MRI as a definitive diagnostic technique. Alzheimer disease. Brain image reveals hippocampal atrophy

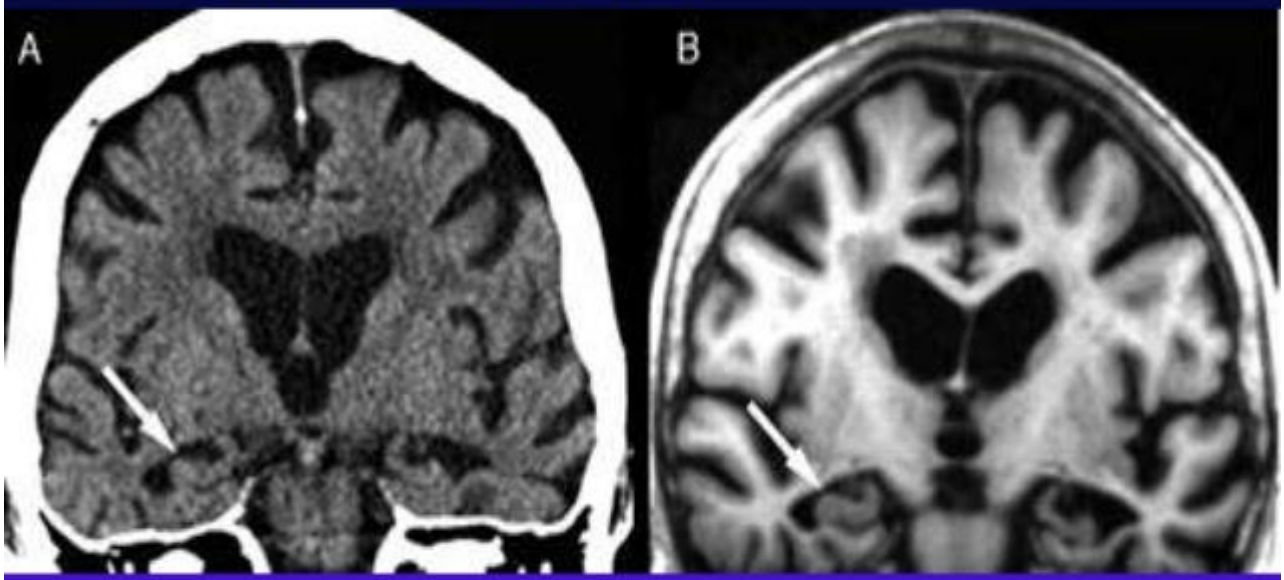




ANATOMICAL BRAIN IMAGING

CT – cerebral tomography

MRI – magnetic resonance imaging

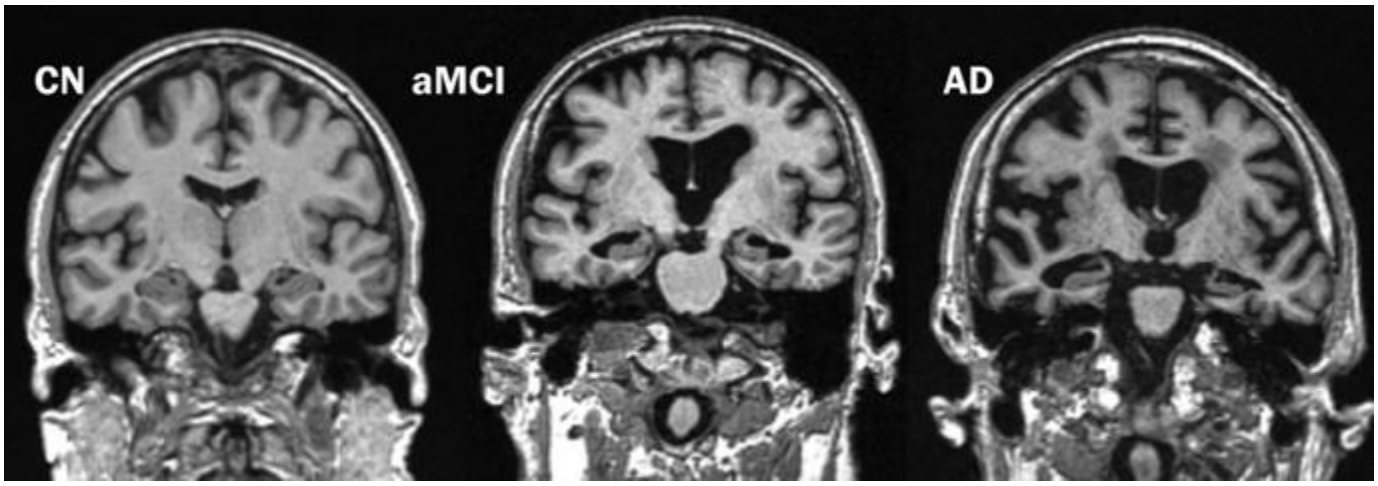


Bilateral medial temporal lobe atrophy (right hippocampus illustrated with arrows) in the same subject with Alzheimer's disease demonstrated on coronal images acquired with: (A) 64 detector row computed tomography scanning; (B) 1.5 tesla MRI volumetric T1 weighted sequence

Extracting information from structural magnetic resonance imaging

Given the large amount of data present in a three-dimensional (3D) sMRI scan, several different methods are employed to condense atrophy information in each patient's scan or assess atrophy over multiple scans of the same individual. The pattern of neurodegeneration seen using sMRI is similar to the progression of neurofibrillary pathology as described by Braak and Braak (Braak *et al*, 1991). The disease usually begins and is ultimately most severe in the medial temporal lobe, particularly the entorhinal cortex and hippocampus. Later (that is, when subjects are in the clinical mild cognitive impairment [MCI] phase), the disease spreads to the basal temporal lobe and paralimbic cortical areas such as the posterior cingulate gyrus and precuneus. The onset of dementia is due to the spread of degenerative atrophy to multimodal association neocortices. Basal forebrain and the dorsal pontomesencephalic areas are also involved. However, unusual variants that do not follow this particular pattern are increasingly recognized. Furthermore, other limbic lobe structures such as posterior cingulate seem to be involved early and consistently in AD. Thr diagram below shows typical MRI scans in cognitively normal (CN) subjects and in patients with MCI or AD. As can been seen in the figure, there is increasing medial temporal atrophy (specifically, the hippocampus and ventricular enlargement) in MCI and AD when compared with CN. Here, we present a brief survey of methods to extract or visualize this information (or both) from 3D sMRI scans of cross-sectional and longitudinal studies.

Figure 2



Progressive atrophy (medial temporal lobes) in an older cognitively normal (CN) subject, an amnestic mild cognitive impairment (aMCI) subject, and an Alzheimer's disease (AD) subject.

Cross-sectional methods

When changes in different individuals are measured cross-sectionally, the most widely used summary measures from sMRI are the following:

1. Visual assessment of scans

Often, visual assessment of the degree of atrophy in the medial temporal lobe is used as a metric to measure disease (Scheltens *et al*, 1992). Visual assessment offers a fast and efficient way to assess MRI scans but does not capture the fine incremental grades of atrophy.

2. Quantitative region of interest-based techniques or volumetry

Volumetry is the most common cross-sectional quantitative metric used in AD. Although traditionally manual tracing of volumes was used, the increase in computational power has led to the development of automated techniques.

2a. Manual tracing

Tracing and quantifying the volume of medial temporal lobe structures (for example, the hippocampus or entorhinal cortex) or posterior cingulate have been traditionally employed in AD and provide an accurate quantitative measure of atrophy (Jack *et al*, 1992). However, manual measurements can be tedious and time-consuming.

2b. Automated and semi-automated techniques

In the recent past, methods have been proposed to automatically parcellate gray matter density or cortical surfaces into regions of interest. These cortical surfaces are used to compute global as well as a regional cortical thickness (that is, combined thickness of the layers in the cerebral cortex). Because automated and semi-automated techniques do not require significant manual intervention, they are extremely useful for large-scale studies.

An advantage of volumetry, such as measuring the hippocampus, is that the measurements describe a known anatomic structure that (in the case of the hippo-campus) is closely related to the pathological expression of the disease and is also functionally related to one of the cardinal early clinical symptoms - memory impairment. However, the disadvantage of using a single region of interest to consolidate 3D information as a disease metric is that it is spatially limited and does not make use of all of the available information in a 3D sMRI.

3. Quantitative voxel-based

These methods assess atrophy over the entire 3D sMRI scan.

3a. Voxel-based analytic techniques

Methods such as voxel-based morphometry (VBM) (Ashburner *et al*, 2000) have been developed to provide a powerful way to test for group-wise comparisons between cross-sectional sMRI scans of diseased group versus normal controls. The typical atrophy patterns seen in subjects with AD or MCI are similar to those of the Braak neurofibrillary staging described above. Although VBM enables visualization of the pattern of neurodegeneration due to disease, the statistical testing portion of VBM is designed only to test for group-wise differences between two groups of subjects and cannot provide a summary measure for each subject, and this makes it inapplicable to diagnosis in individual subjects.

3b. Automated individual subject diagnosis

Several investigators have recently turned their attention to multivariate analysis and machine learning-based algorithms that use the entire 3D sMRI data to form a disease model against which individual subjects may be compared. These scores typically are computed for each new incoming scan (that is, test scan) on the basis of the degree and the pattern of atrophy in comparison with the scans of a large database of well-characterized AD and cognitively normal subjects (Vemuri *et al*, 2008).

Longitudinal methods

Because accelerating tissue loss is a hallmark of neuro-degenerative disease, serial sMRI scans often are analyzed to measure disease progression. Even though cross-sectional measures can be

employed to obtain a summary measure from sMRI at every time point, these measures have unnecessary variability due to inherent noise associated with each individual measurement. Therefore, specific techniques have been developed to extract tissue loss information from serial sMRI scans. In these techniques, all pairs of sMRI scans are registered to each other and brain loss between scans is quantified and this reduces the variability.

Global atrophy quantification

One of the earliest methods developed to quantify the global percentage change in brain volume between two scans was boundary shift integral (BSI) (Freeborough, 1997). BSI determines the total volume through which the surface of the brain has moved between scans acquired at two time points (that is, the brain volume decreases and the volume of the ventricles increases). One of the most sensitive global measures for measuring the rates of brain atrophy is the ventricular change measure using BSI (Jack *et al*, 2004). This is because the ventricular boundary on sMRI (T1-weighted images) provides a good contrast for the delineation of the ventricular surface with more accuracy when compared with brain volume and hippocampal volume.

Tensor-based morphometry

Unlike BSI, which analyzes only spatial shift in the brain surfaces, TBM provides a 3D profile of voxel-level brain degeneration. Here, the term TBM is used to describe 3D voxel-based methods that can be employed to observe how the disease progresses in the brain as a result of the underlying pathological changes (Thompson *et al*, 2007).

Role of structural magnetic resonance imaging in Alzheimer's disease and mild cognitive impairment

These are the different roles in which sMRI can be employed as an AD biomarker. When MCI involves primarily memory complaints and deficits, it is often considered a prodromal stage of AD. Here, we will also discuss the role of sMRI in MCI in addition to AD.

1. Early diagnosis of Alzheimer's disease and mild cognitive impairment

The typical reductions of hippocampal volume in MCI with an average Mini-Mental State Exam (MMSE) score of 25 are 10% to 15% and in AD with an average MMSE score of 20 are 20% to 25% (Scahill *et al*, 2002). Measuring these significant reductions (due to AD) in the medial temporal lobe can be extremely useful for early diagnosis of AD and MCI. At present, diagnostic criteria for AD are based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), which are based primarily on clinical and psychometric assessment and do not use quantitative atrophy information available in sMRI scans. However, there is a proposal to add reliable biomarkers to the diagnostic criteria (Shi *et al*, 2002). One of the suggested features is the volume loss of medial temporal structures since measures of sMRI atrophy have accuracies of 70% to 90% in AD and 50% to 70% in amnestic MCI in distinguishing them from age-matched controls (Shi *et al*, 2002). All of the above-mentioned cross-sectional methods can be used as diagnostic metrics for AD and MCI.

2. Predicting the risk of progression in mild cognitive impairment and cognitively normal

Although there is considerable variability of progression rates in MCI to AD, it has been observed that an average of about 10% to 15% of subjects with MCI, specifically of the amnestic type, annually progress to AD (Dubois *et al*, 2007). Because pathological changes occur before the onset

of clinical symptoms, biomarkers can aid in the prediction of risk of progression in MCI and CN. A recent meta-analysis showed that hippocampal volume can detect an average of approximately 73% of MCI subjects who progress to AD (Petersen, 2007). Several studies using both cross-sectional methods 1 and 2 above have shown that atrophy seen on MRI can predict the risk of progression to AD with good accuracy.

3. Evaluating disease progression

Charting structural changes in the brain over time is important in monitoring the progression of the disease (Fox *et al*, 1997). Tracking the disease progression is especially important in patients with MCI and cognitively normal subjects since atrophy rates can predict subsequent clinical progression in both groups. The metrics that are most often used for evaluating or tracking disease progression are increase in ventricular volume and decrease in brain volume over time. These measures are more sensitive than cross-sectional measures in capturing changes over time since all scans of the same subject are registered together to reduce inter-scan variability.

4. Measuring the efficacy of therapeutics

Several investigators have shown that the lower variance in the serial sMRI measurements compared with clinical measures of cognition and function could permit clinical trials to be performed with smaller sample sizes than would be possible using traditional clinical instruments (Jack *et al*, 2003) (Fox *et al*, 2000) (Vemuri *et al*, 2010). At present, AD biomarkers have not yet been validated as surrogate endpoints for regulatory purposes and therefore cannot be used as the primary indicators of efficacy. However, the impact of interventions on these biomarkers has been evaluated in a few trials and was found to be potentially useful in capturing the pharmacodynamic effects. The efficacy of donepezil, a cholinesterase inhibitor, was evaluated using serial sMRI (

Hashimoto *et al*, 2005) (Krishnan *et al*,2003) and was found to possibly be neuro-protective in nature since there was some evidence for decreased disease progression on the basis of sMRI trophy. In a different study, it was observed that subjects immunized with Aβ antibody responders had a more rapid volume loss than placebo patients during a phase IIa immunotherapy trial that was prematurely terminated owing to meningoencephalitis in a subset of patients (Fox *et al*, 2005). In addition to evaluating therapeutic efficacy, atrophy on sMRI can be used to select at-risk MCI subjects for clinical trials. While longitudinal methods are useful for testing efficacy of therapeutics, cross-sectional methods are most suited for sample enrichment.

5. Screening in clinical trials

MRI is routinely used at two stages in clinical trials. The first is screening at baseline for inclusion/exclusion. This includes identifying subjects with imaging evidence of conditions that are exclusionary (for example, hemispheric infarction or prior evidence of cerebral hemorrhage). Also, anti-amyloid trials commonly will exclude subjects with micro-hemorrhages that exceed a specified number. Either long echo time gradient echo or susceptibility-weighted imaging sequences are used for micro-hemorrhage identification. MRI is also used for safety screening during the study. Conditions that are of interest are evidence of new micro-hemorrhage and vasogenic edema. FLAIR (fluid-attenuated inversion recovery) and diffusion imaging are used to identify the latter condition.

6. Differential diagnosis of dementia subtypes

Given that pathology does not always map onto the clinical expression of the disease and has considerable clinical heterogeneity, biomarkers such as sMRI can aid in the differential diagnosis of dementia types. The absence of significant medial temporal lobe atrophy in dementia with Lewy

bodies (Mckeith *et al*, 2005) and vascular dementia (Barber *et al*, 1999) significant frontal lobe atrophy in behavioral variant fronto-temporal dementia (Duara *et al*, 1999), or pronounced asymmetrical temporal lobe atrophy in semantic dementia (Galton *et al*,2005) can be used to separate these non-AD dementias from AD. Diffusion imaging and FLAIR are useful in identifying both cerebrovascular disease and prion disease. MRI is useful in identifying structural contributors to cognitive impairment such as hemorrhage or evidence of major head trauma. Differential diagnosis of dementias using sMRI will be particularly helpful when therapeutics become readily available.

7. Mechanistic inferences into the disease process

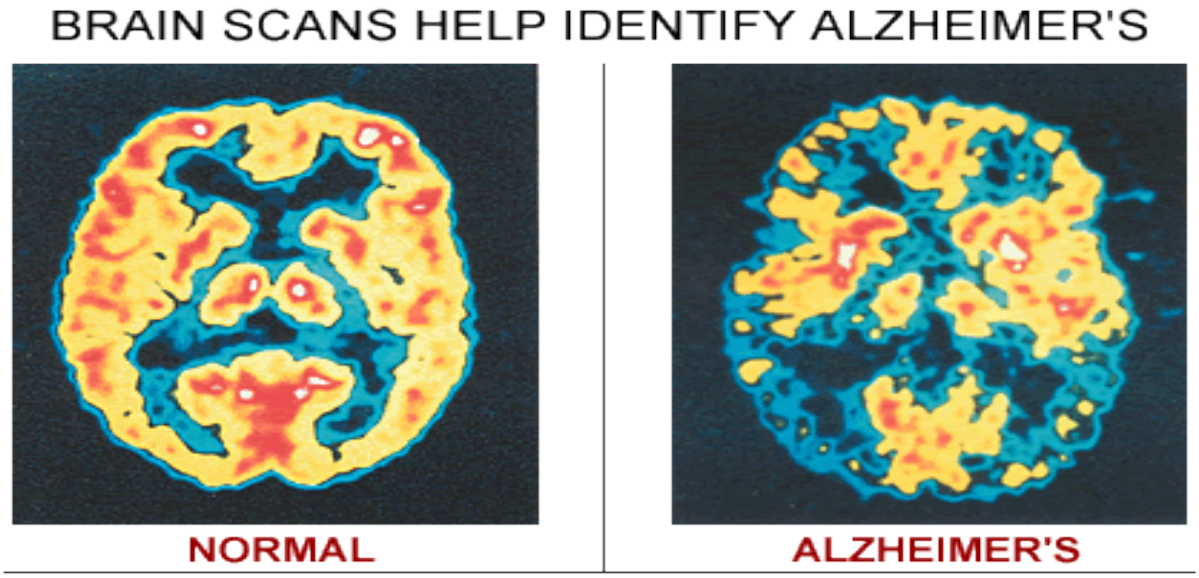
Using sMRI as an independent biomarker of neurodegeneration aides in understanding relationships between cognition and neurodegeneration in AD. This has led to insights into disease mechanisms in AD. In the model shown in the figure above from Jack and colleagues (Jack *et al*, 2010) the conclusion that neurodegeneration is more proximately associated with cognitive decline was derived from several MRI studies

Limitations of Structural MRI in AD

Structural MRI lacks molecular specificity. It cannot directly detect the histopathological hallmarks of AD (amyloid plaques or neurofibrillary tangles) and as such it is downstream from the molecular pathology (Charles *et al*., 2014). As the name implies, structural MRI cannot assess function; this is provided with increasing sophistication by functional MRI and PET.

POSITRON EMISSION TOMOGRAPHY(PET)

Positron Emission Tomography (PET) scans are used to measure the concentration of particular molecules in the brain. For a PET scan, a special molecule called a ligand is injected into the body and attaches to particular molecules of interest in the brain. The ligand emits a small amount of radiation that is picked up by the scanner, so we can see how much of the molecule is in the brain. Although the dose of radiation is small as a precaution you may be advised to avoid prolonged close contact with pregnant women, babies or young children for a few hours after a PET scan.



Brain scans done with Positron Emission Tomography (PET) show how Alzheimer's affects brain activity. The left image shows a normal brain, while the right is from a person with Alzheimer's. The blue and black areas in the right image indicate reduced brain activity resulting from the disease.

Images courtesy of Alzheimer's Disease Education and Referral Center, National Institute on Aging

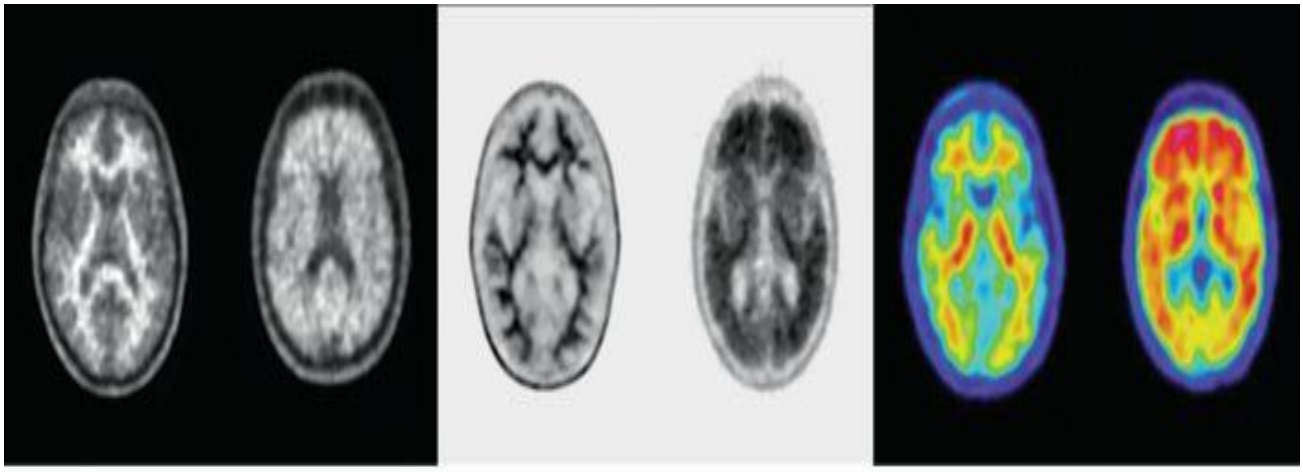
There are different types of PET scan:

An amyloid-PET scan measures the build-up of abnormal amyloid protein in the brain, one of the key hallmarks of Alzheimer's disease.

An FDG (FLOUORODEOXYGLUCOSE)-PET scan measures the concentration of glucose in the brain, revealing how the brain is using energy. These scans reveal aspects of how the brain is working that can't be seen in any other way.

AMYLOID PET SCAN

An amyloid-PET scan measures the build-up of abnormal amyloid protein in the brain, one of the key hallmarks of Alzheimer's disease. A negative amyloid PET scan result indicates a reduced likelihood that cognitive impairment is caused by AD, but a positive scan result does not establish a diagnosis of AD. However, amyloid PET imaging must be performed in a setting of a clinically suspected AD because there is a relative low SP.



Three pairs of images from six brain amyloid PET scans. Each pair utilizes a different PET imaging ligand. "Negative" means the person has little or no beta amyloid neuritic plaques in the brain. "Positive" indicates the person has moderate to high levels of beta amyloid neuritic plaques in the brain. These images do not reflect IDEAS-Study participants.

Photo Credit: Alzheimer's Association / IDEAS-Study. The images are used with permission from left to right by Piramal Imaging, Avid Radiopharmaceuticals and GE Healthcare.

The Limitations of Amyloid PET in AD

Major deterrents to the widespread use of amyloid PET remain cost and availability. Availability has been improved by the development of F-18-labeled agents that can be distributed to PET scanners not associated with a cyclotron. Cost remains an issue, especially where CSF measurement of Aβ42 can provide very similar information when the question is simply the presence or absence of brain Aβ deposition. Being an early event in the pathogenesis of AD, amyloid PET is not a good surrogate marker of progression during the clinical stage of the disease (Engler *et al*. 2006; Kadir *et al*. 2010). This role is filled much better by structural MRI and FDG PET (Jack *et al*. 2010). Similarly, amyloid imaging gives much more of a binary diagnostic read out than techniques such as MRI and FDG PET. That is, amyloid imaging has a certain specificity for the pathology of AD, but when that pathology is absent, a negative amyloid PET scan will be

identical regardless of the non-AD etiology of the dementia. In contrast, MRI and FDG PET may give an indication of a frontotemporal or vascular pathology when an amyloid PET scan would be ambiguously negative in both cases. The threshold of sensitivity of amyloid PET has yet to be precisely determined, but it is clear that some level of amyloid deposition is histologically detectable prior to the in vivo signal becoming "positive" (Cairns *et al*. 2009).

FLUORODEOXYGLUCOSE (FDG) PET IN AD

Basics of FDG PET as Applied to AD

Brain FDG PET primarily indicates synaptic activity. Because the brain relies almost exclusively on glucose as its source of energy, the glucose analog FDG is a suitable indicator of brain metabolism and, when labeled with Fluorine-18 (half-life 110 min) is conveniently detected with PET. The brain's energy budget is overwhelmingly devoted to the maintenance of intrinsic, resting (task-independent) activity, which in cortex is largely maintained by glutamaturgic synaptic signaling (Sibson *et al*. 1997). FDG uptake strongly correlates at autopsy with levels of the synaptic vesicle protein synaptophysin (Rocher *et al*. 2003). Hence, FDG PET is widely accepted to be a valid biomarker of overall brain metabolism to which ionic gradient maintenance for synaptic activity is the principal contributor (Schwartz *et al*. 1979; Magistretti, 2006).

The Limitations of FDG PET in AD

FDG PET is relatively expensive and, like all PET techniques, has more limited availability, although its use in oncology has dramatically increased availability in the USA over the past decade. It requires intravenous access and involves exposure to radioactivity, although at levels well below significant known risk.

SPECT SCAN

A single-photon emission computerized tomography (SPECT) scan allows us to analyze the function of some of the internal organs. A SPECT scan is a type of nuclear imaging test, which means it uses a radioactive substance and a special camera to create 3-D pictures. The most common uses of SPECT are to help diagnose or monitor brain disorders, heart problems and bone disorders.

SPECT can be helpful in determining which parts of the brain are being affected by:

- Dementia
- Clogged blood vessels
- Seizures
- Epilepsy
- Head injuries

SPECT SCAN AND ALZHEIMER'S DISEASE

Single-photon emission computed tomography (SPECT) scanning is not commonly used to assess Alzheimer disease. SPECT scanning is useful in the diagnostic assessment of Alzheimer disease if standardized and semi quantitative techniques are used. SPECT does have diagnostic value, particularly in differentiating Alzheimer disease from frontotemporal dementia and normal control subjects. However, it should not be used in isolation, but rather as an adjunct, and interpreted in the context of clinical information test results.

REFERENCES

Braak H, Braak E: Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991, 82: 239-259. 10.1007/BF00308809.

Duara R, Loewenstein DA, Potter E, Appel J, Greig MT, Urs R, Shen Q, Raj A, Small B, Barker W, Schofield E, Wu Y, Potter H: Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. Neurology. 2008, 71: 1986-1992. 10.1212/01.wnl.0000336925.79704.9f.

Fagan AM, Mintun MA, Shah AR, Aldea P, Roe CM, Mach RH, Marcus D, Morris JC, Holtzman DM 2009. Cerebrospinal fluid tau and ptau$_{181}$ increase with cortical amyloid deposition in cognitively normal individuals: Implications for future clinical trials of Alzheimer's disease. EMBO Mol Med 1: 371–380.

Fox NC, Scahill RI, Crum WR, Rossor MN: Correlation between rates of brain atrophy and cognitive decline in AD. Neurology. 1999, 52: 1687-1689.

Gross AL, Jones RN, Habtemariam DA, Fong TG, Tommet D, Quach L, Schmitt E, Yap L, Inouye SK. Delirium and Long-term Cognitive Trajectory Among Persons With Dementia. Arch Intern Med. 2012 Sep 24;172(17):1324-31.

Honjo K, Black SE, Verhoeff NP. Alzheimer disease, cerebrovascular disease, and the β-amyloid cascade. Can J Neurol Sci. 2012 Nov;39(6):712-28. Review.

Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ: Hypothetical model of dynamic biomarkers of the Alzheimer's

pathological cascade. Lancet Neurol. 2010, 9: 119-128. 10.1016/S1474-4422(09)70299-6.

Kadir A, Almkvist O, Forsberg A, Wall A, Engler H, Langstrom B, Nordberg A 2010. Dynamic changes in PET amyloid and FDG imaging at different stages of Alzheimer's disease. Neurobiol Aging (in press) 10.1016/j.neurobiolaging.2010.06.015.

Karow DS, McEvoy LK, Fennema-Notestine C, Hagler DJ Jr, Jennings RG, Brewer JB, Hoh CK, Dale AM 2010. Relative capability of MR imaging and FDG PET to depict changes associated with prodromal and early Alzheimer disease. Radiology 256: 932–942.

Kemppainen NM, Aalto S, Karrasch M, Nagren K, Savisto N, Oikonen V, Viitanen M, Parkkola R, Rinne JO 2008. Cognitive reserve hypothesis: Pittsburgh Compound B and fluorodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. Ann Neurol 63: 112–118.

Kloppel S, Stonnington CM, Chu C, Draganski B, Scahill RI, Rohrer JD, Fox NC, Jack CR Jr, Ashburner J, Frackowiak RS 2008. Automatic classification of MR scans in Alzheimer's disease. Brain 131: 681–689.

Langbaum JB, Chen K, Lee W, Reschke C, Bandy D, Fleisher AS, Alexander GE, Foster NL, Weiner MW, Koeppe RA, *et al*. 2009. Categorical and correlational analyses of baseline fluorodeoxyglucose positron emission tomography images from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Neuroimage 45: 1107–1116.

Rabinovici GD, Furst AJ, O'Neil JP, Racine CA, Mormino EC, Baker SL, Chetty S, Patel P, Pagliaro TA, Klunk WE, *et al*. 2007. ^{11}C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. Neurology 68: 1205–1212.

Remy F, Mirrashed F, Campbell B, Richter W 2004. Mental calculation impairment in Alzheimer's disease: A functional magnetic resonance imaging study. Neurosci Lett 358: 25–28.

Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, Kuiper M, Steinling M, Wolters EC, Valk J: 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. 10.1136/jnnp.55.10.967.

Shaffer JL, Petrella JR, Sheldon FC, Choudhury KR, Calhoun VD, Coleman RE, Doraiswamy PM; zheimer's Disease Neuroimaging Initiative. Predicting Cognitive Decline in Subjects at Risk for Alzheimer Disease by Using Combined Cerebrospinal Fluid, MR Imaging, and PET Biomarkers. Radiology. 2013 Feb;266(2):583-91. doi: 10.1148/radiol.12120010. Epub 2012 Dec 11.

Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N (2010). "A meta-analysis of cytokines in Alzheimer disease". Biol Psychiat 68 (10): 930-941.

World Health Organization. WHO Mental Health Gap Action Programme (mhGAP) 2008.