UNIVERSITI PUTRA MALAYSIA

AGRICULTURE • INNOVATION • LIFE

# Exploring the role of molecular imaging in neural circuitry of cognition and ageing

**DR. SUBAPRIYA SUPPIAH**

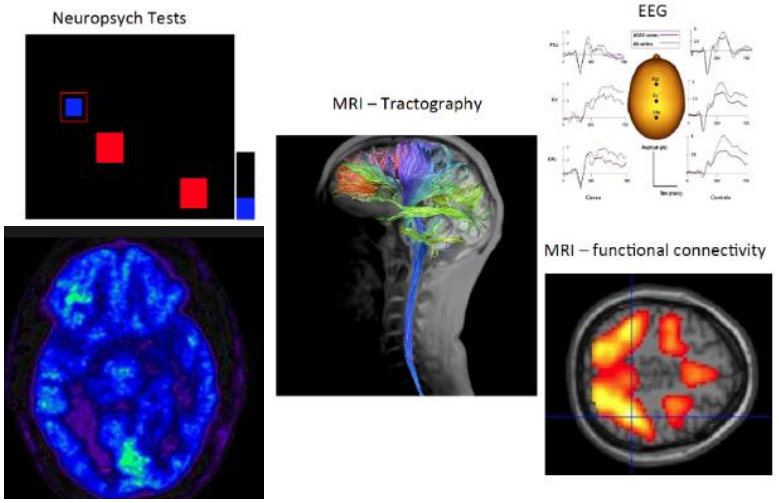
**Consultant Radiologist , PET/CT Fellow and Deputy Director**

**Pusat Pengimejan Diagnostik Nuklear, UPM**

# Cognitive Neuroimaging



- Mapping different regions of the brain
- With relations to their functions
- Enables better understanding of disease pathophysiology, designing treatment and intervention plan, innovations in brain-computer interphase (BCI)e.g. in robotic rehabilitation for stroke

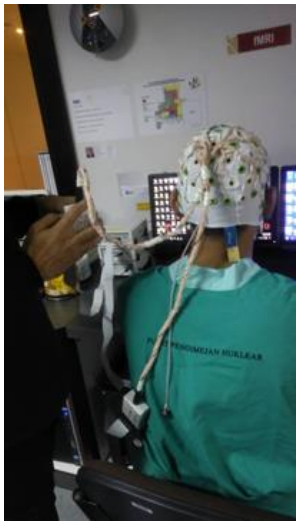


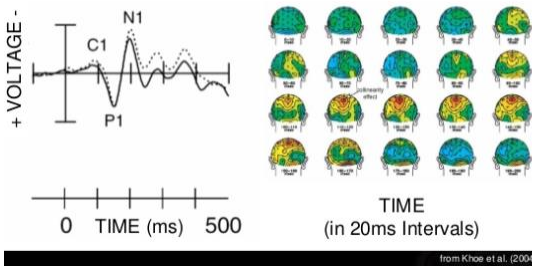
# Modalities for Neuroimaging



Assessment of the human brain function:

1. Electroencephalography (EEG)
2. Magnetoencephalography (MEG)
3. Transcranial Magnetic stimulation (TMS)
4. Structural MRI
5. Positron Emission Tomography (PET)
6. Functional MRI
7. Simultaneous EEG-fMRI





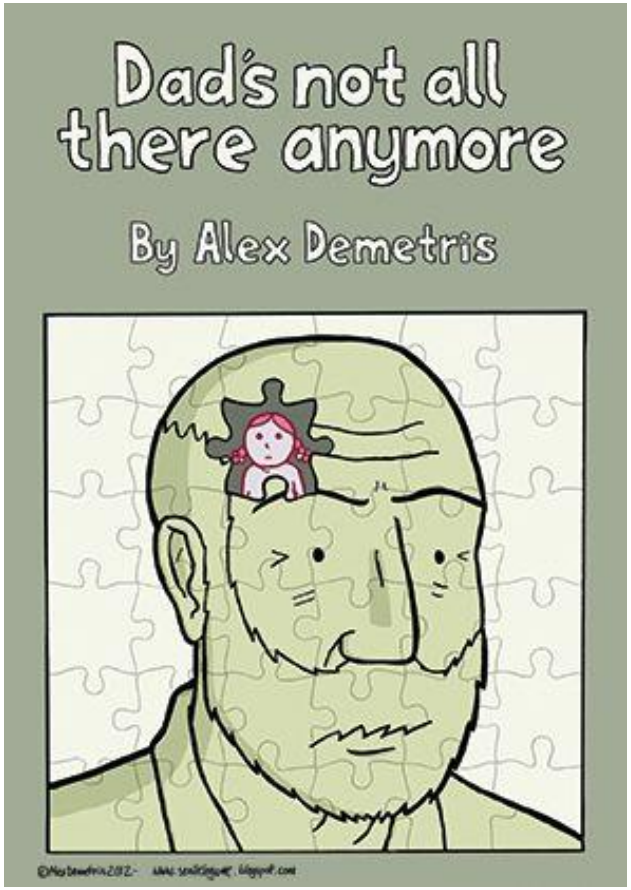

http://neoreviews.aappublications.org/content/16/9/e544

# Common indications for neuroimaging

- Stroke
- Epilepsy
- Brain tumour
- Impaired cognitive function (Neurocog d/o, AD; exposure to extreme high altitude)
- Neuropsychiatric disorders (Schizophrenia, MD, addiction)

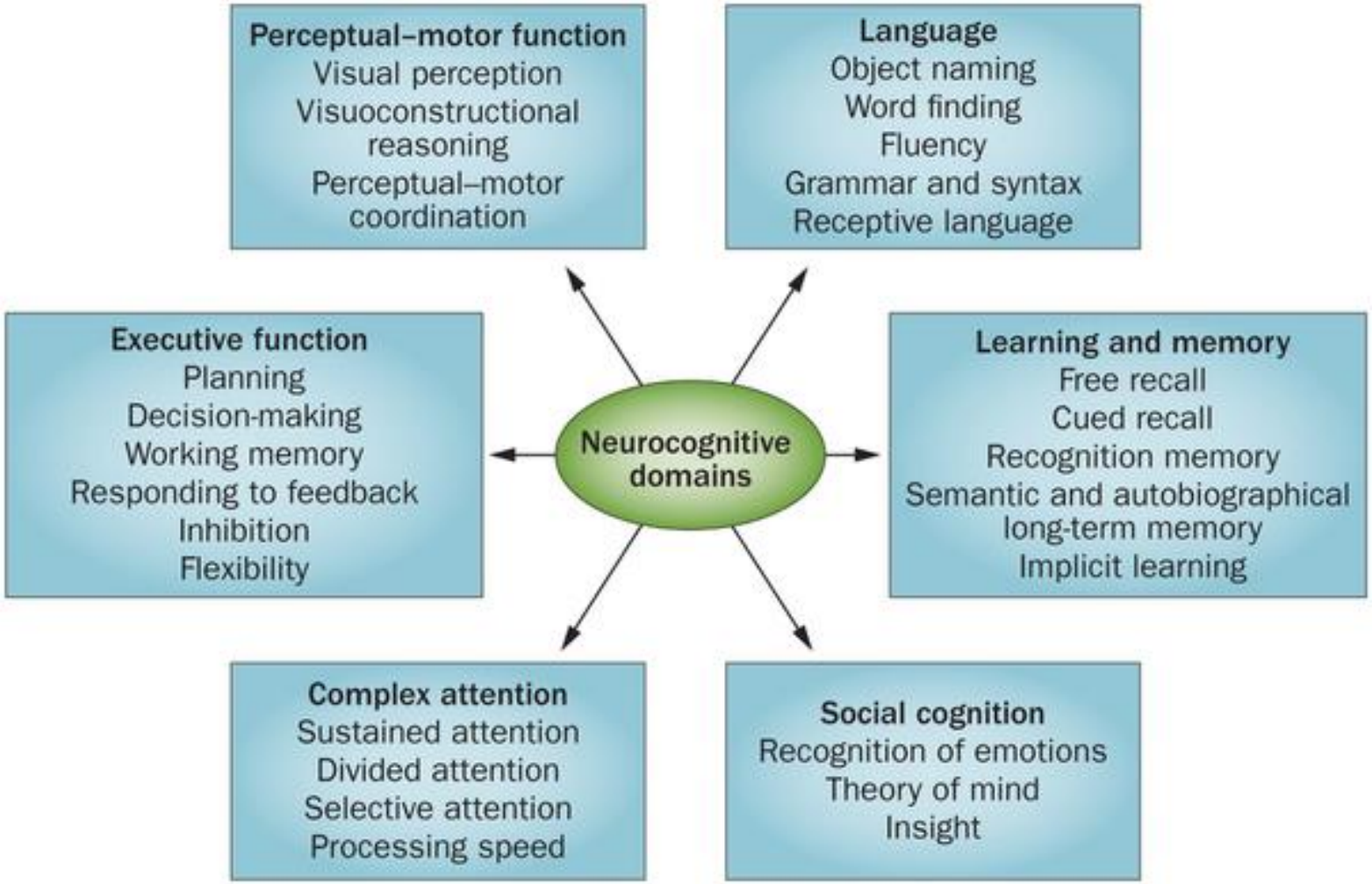
# Terminology

- Dementia, Demented
- Neurocognitive Disorders
- Stigma



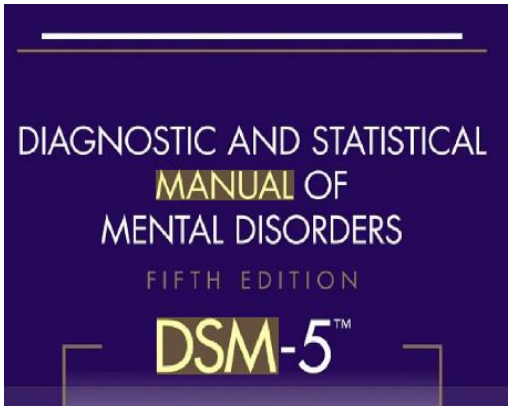
# Neurocognitive Function

AGRICULTURE • INNOVATION • LIFE



# CLINICAL DIAGNOSIS AD





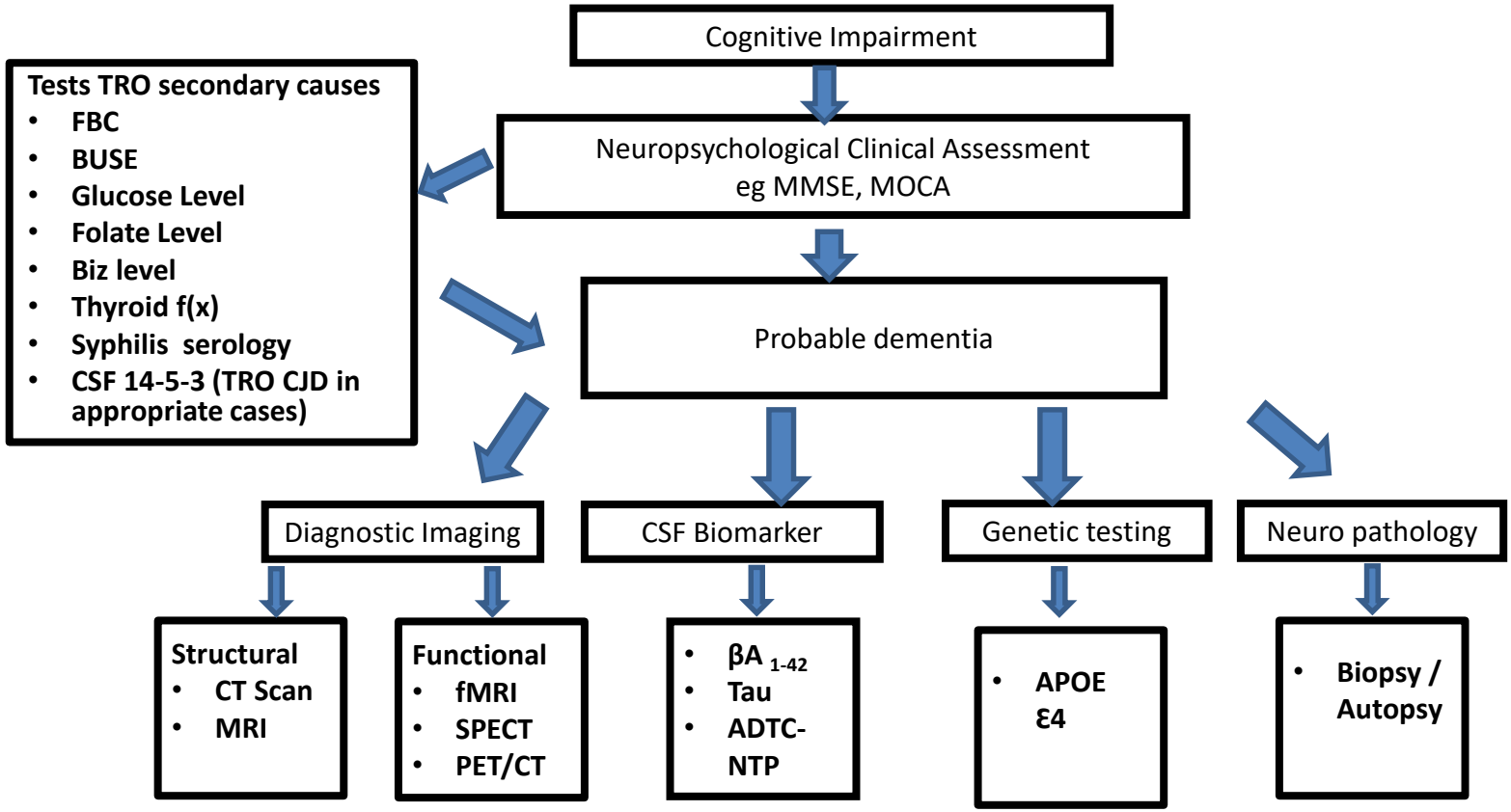

Major Neurocognitive Disorders

Alzheimer's Disease subtype

1.Progressive and signif. reduction in cognitive function from previous level of cognition
2.Reduced performance in a neuropsychiatric test (objective assessment)
3.Significant impairment in the ability to independently perform cognitive activities of daily living
4.In the absence of delirium, other mental illnesses or medical conditions

(American Psychiatric Association, 2013) & (DSM-V)

# Clinical Work-up for AD

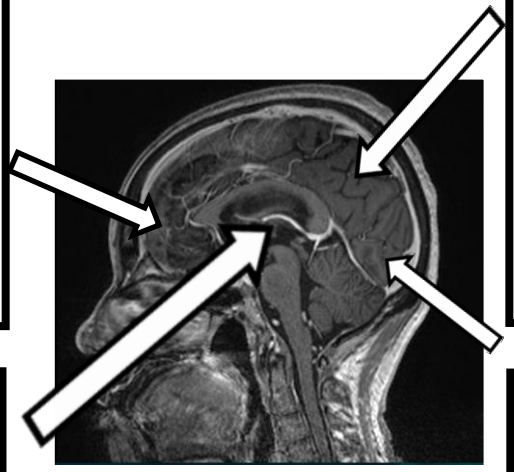


# Major Neurocognitive Disorders

## SUBTYPES OF DEMENTIA

**Fronto temporal dementia (FTD)**

Onset: Fluctuating Memory
Initial Sx: Personality And Behaviour Changes, Multisensory Agnosia
Imaging :
MRI - Atrophy In Focal Frontal Anterior Temporal
SPECT – Hypoperfusion In Fronto-Temporal Lobe, Spares Posterior Parietal Lobe
Pathology: Tau Inclusion Bodies, Pick Bodies



**Alzheimer's Disease (AD)**

Onset: > 65 years old
Initial Sx: Memory loss, language deficit
Imaging:
MRI – diffuse/ posteriorly predominant/ hippocampal atrophy
SPECT – Hypoperfusion in posterior temporo-parietal lobe
PET – positive amyloid deposition in posterior temporo-parietal lobe
Pathology: Senile plaques, NFTs

**Vascular Dementia (VD)**

Onset: Can be sudden in onset
Initial Sx: Focal neurological signs, signs of vascular disease(stroke/ weakness)
Imaging: MRI –may identify areas of infarcts, WM lesions/ hyperintensities on T2Wi
SPECT – Multiple/ focal areas of hypoperfusion corresponding to areas of infarcts.
PET – negative for amyloid deposition
Pathology: Areas of ischaemia/ infarcts.

**Dementia with Lewy bodies (DLB)**

Onset:
Initial Sx: Parkinsonism, visual hallucination, fluctuating cognitive functions
Imaging:
MRI - less atrophy compared to AD.
SPECT - Hypoperfusion in temporal & occipital lobe
PET – positive amyloid deposition in posterior \ temporo-parietal lobe
Pathology: α synuclein, Lewy bodies

# Diagnostic Performance of Clinical Assessment and other tests

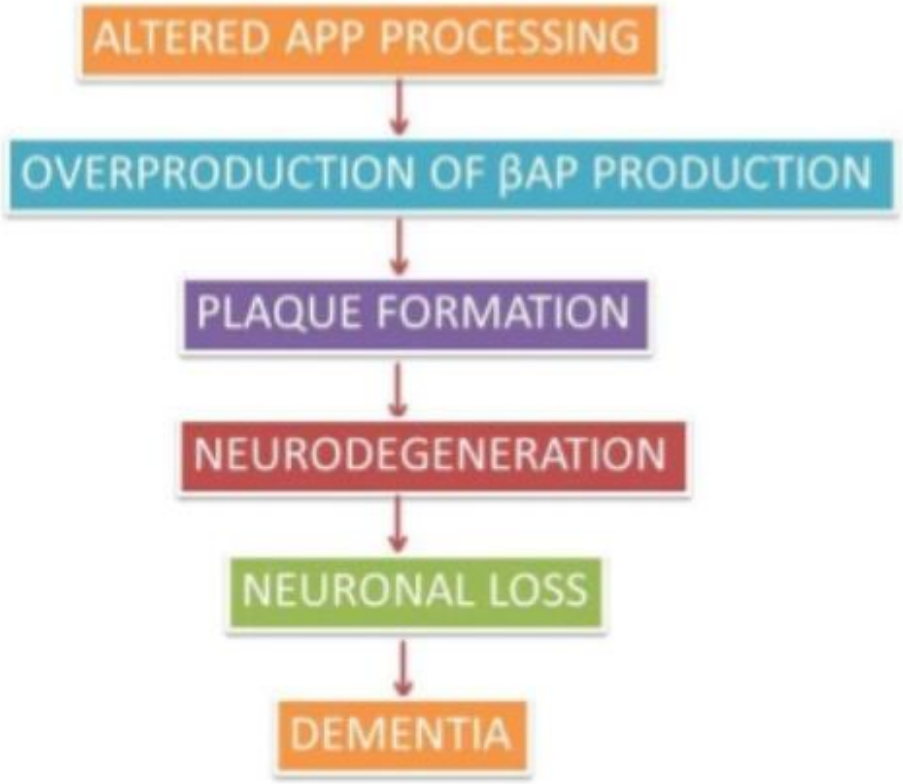
AGRICULTURE • INNOVATION • LIFE

| Sub types | Clinical Assessment(%) | |
|---|---|---|
| | Sensitivity | Specificity |
| AD | 81 | 70 |
| VA | 89 | 89 |
| DLB | > 50 | <75 |
| FTD | 63-73 | 97-100 |

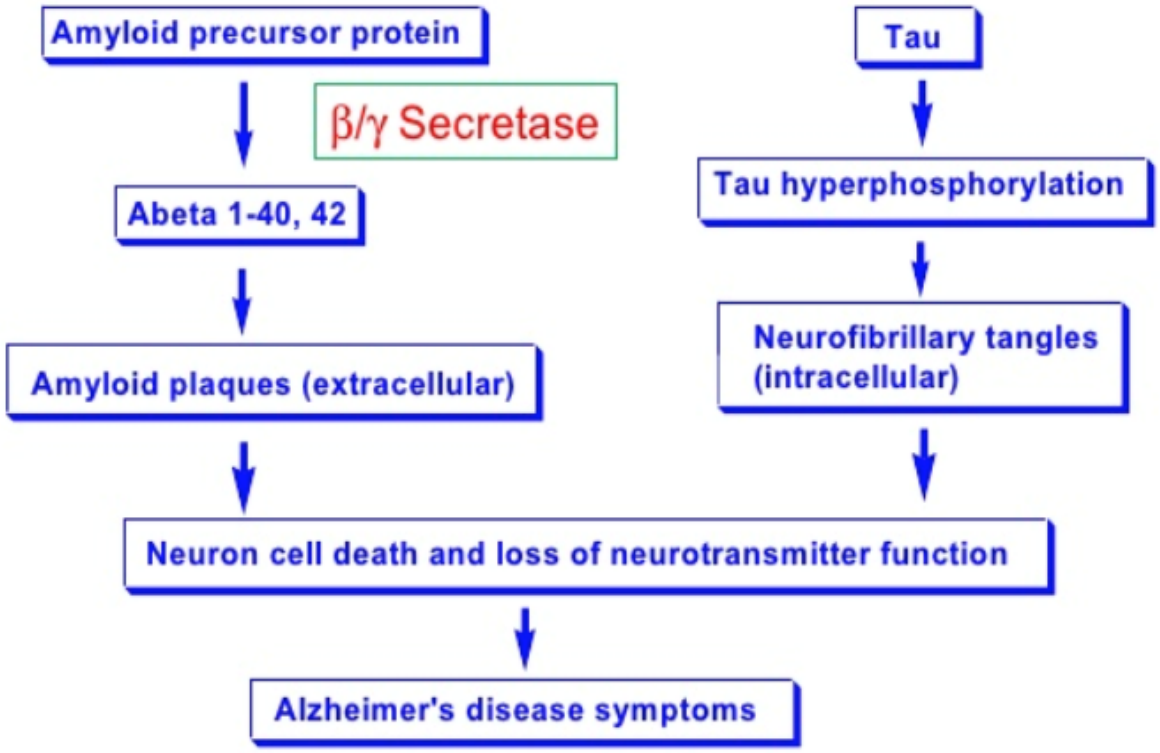
| Test | Sensitivity (%) | Specificity (%) |
|---|---|---|
| Clinical Assessment | 81 | 70 |
| MRI | 95 | 40 |
| SPECT | *71.5 | 78.2 |
| FDG-PET | 93 | 63 |
| APOE Ɛ4 | 89 | 65 |

*Dougall Am J Geriatr Psychiatr. 2004
**Hoffman. J Nucl Med 2000

# Pathophysiology



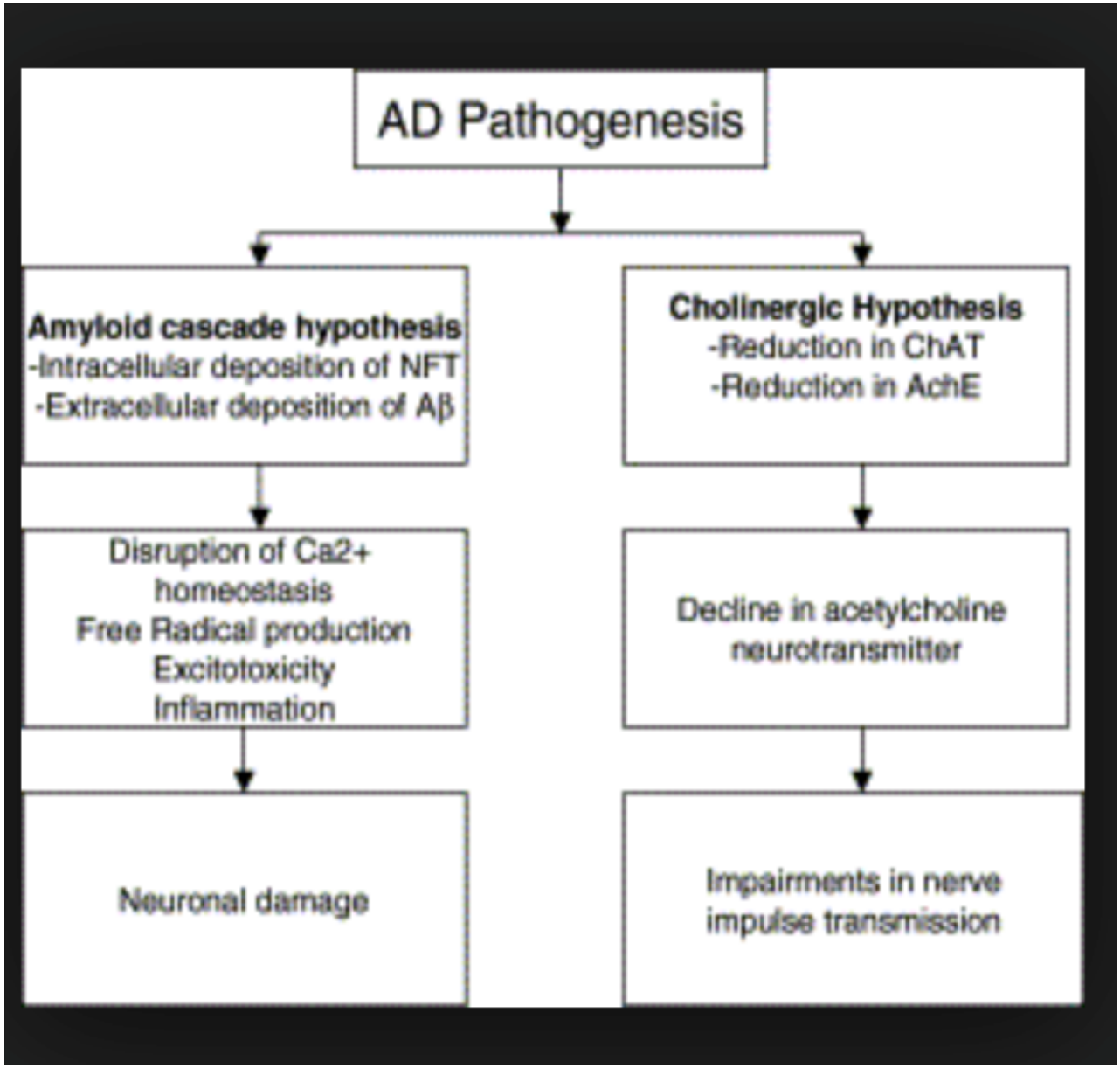
# Alzheimer's Disease Pathophysiology




*Alzheimer's Disease is a progressive, devastating and incurable illness*

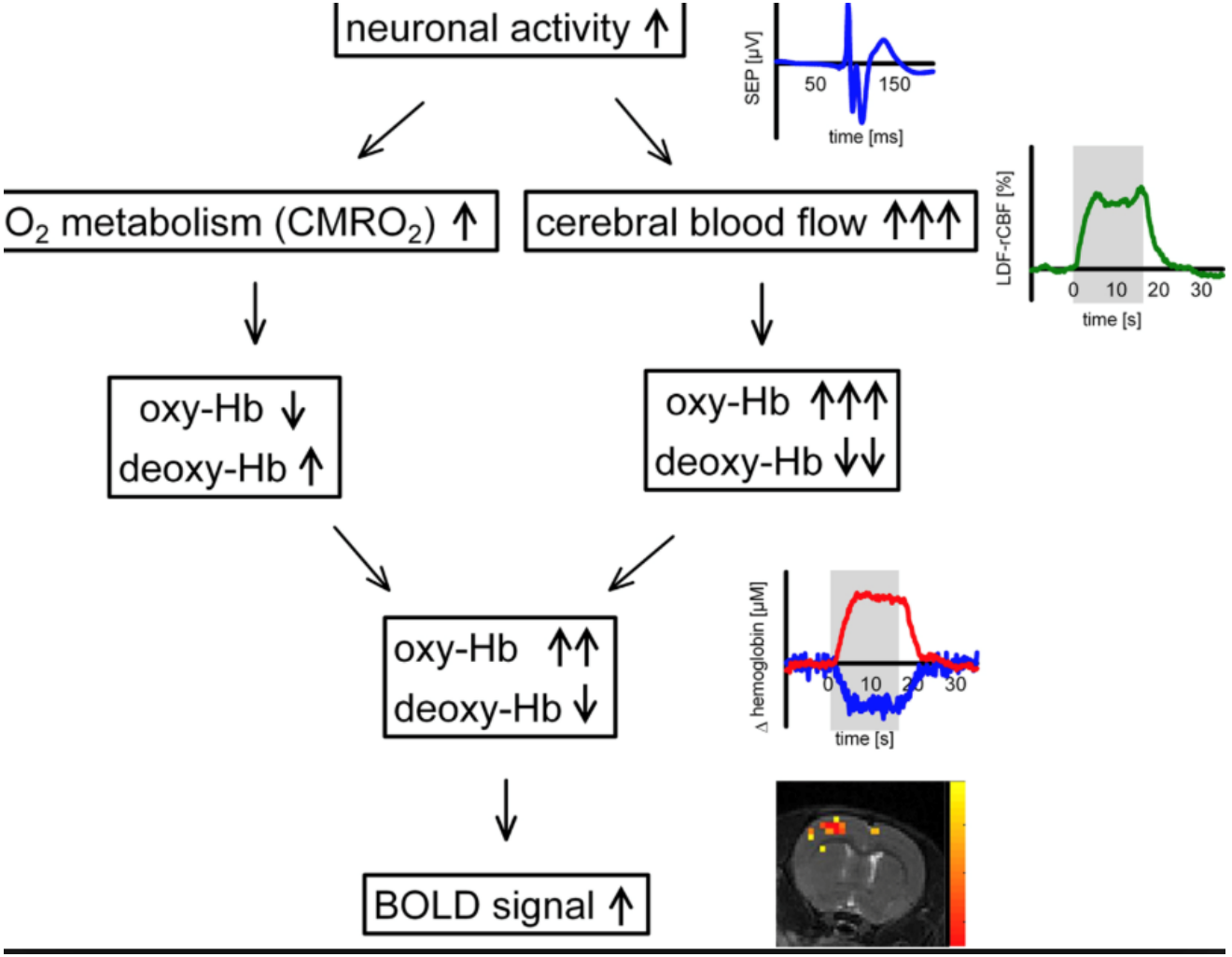
*Some 4.5 million Americans are affected at a cost of $100 billion a year*

Nitasha Manchanda, Alzheimer's Disease, *Decision Resources*, June 2007




Sciencedirect.com

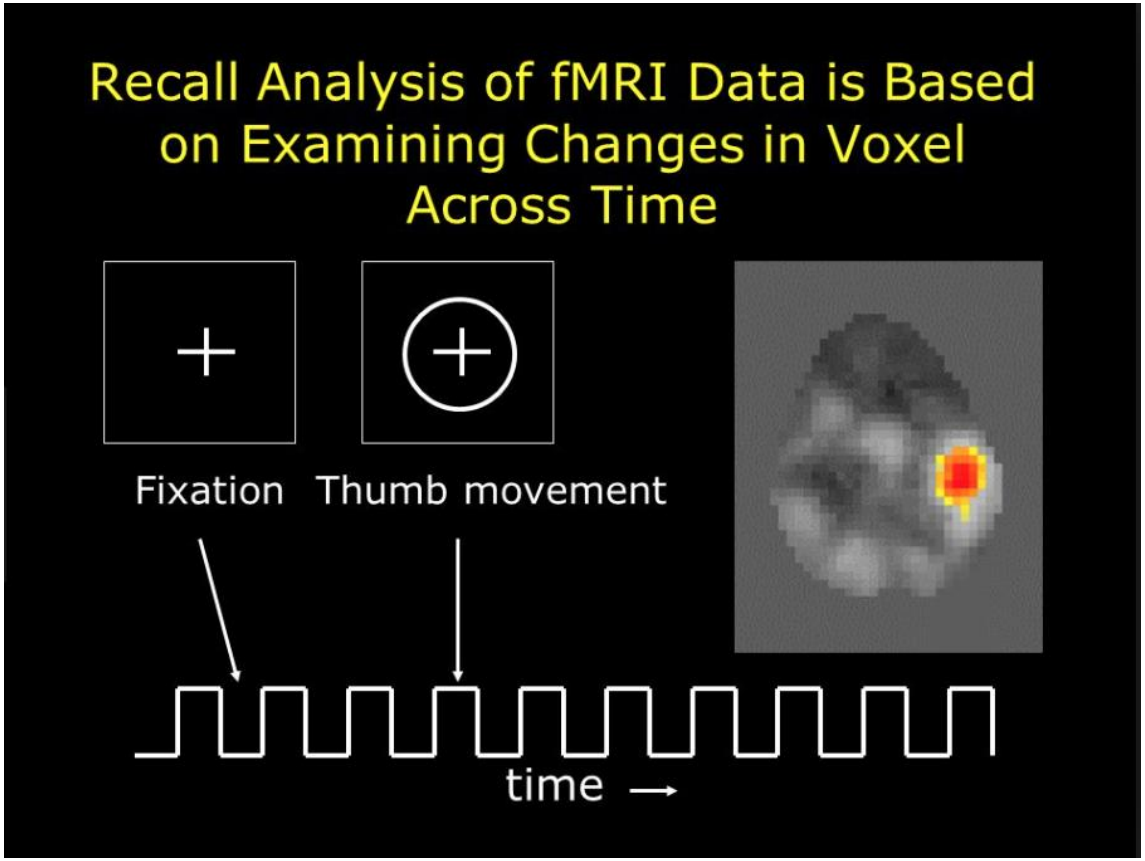
# Molecular Imaging -fMRI




Lindauer 2010.Frontiers in Neuroenergenics

# Molecular Imaging

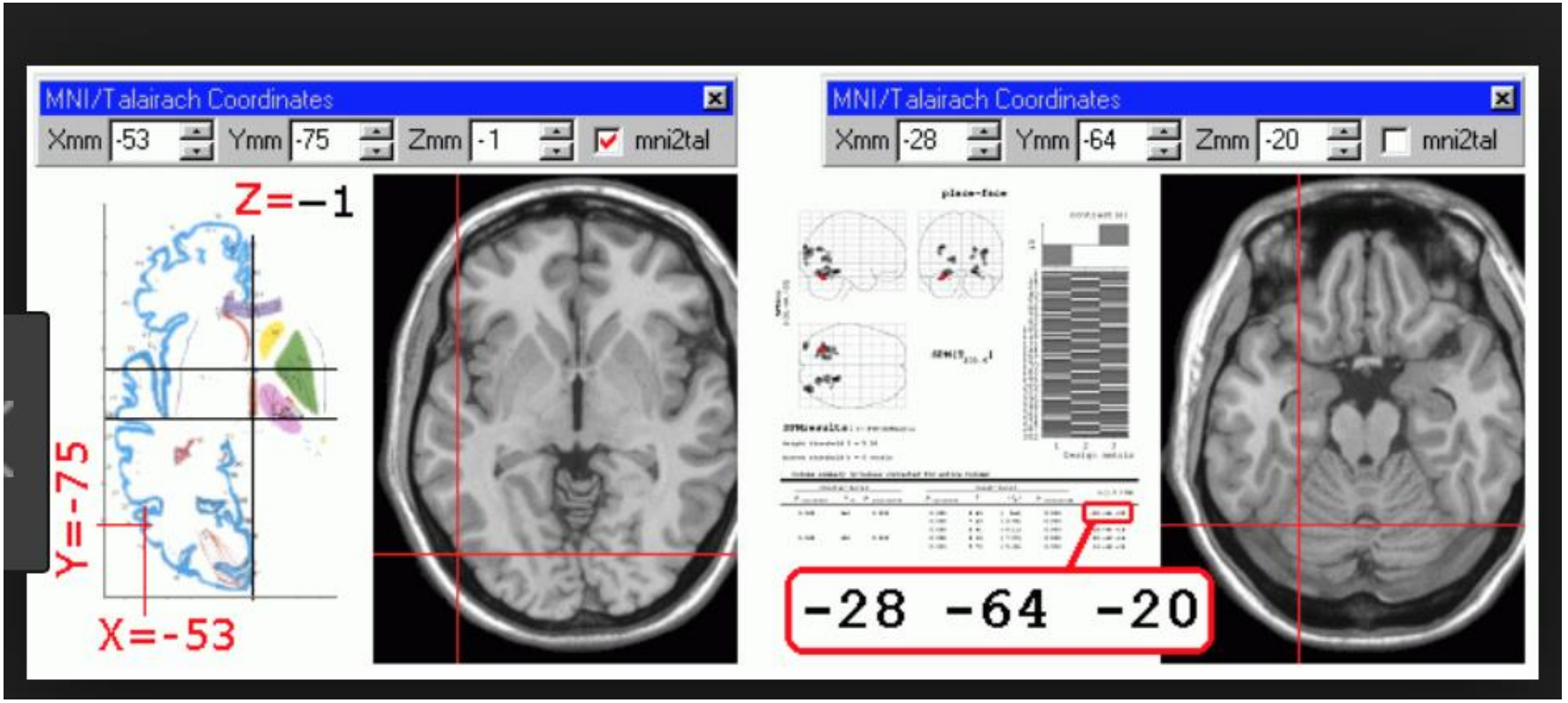





https://slideplayer.com/slide/6955770/ John VanMeter

# Molecular Imaging -fMRI

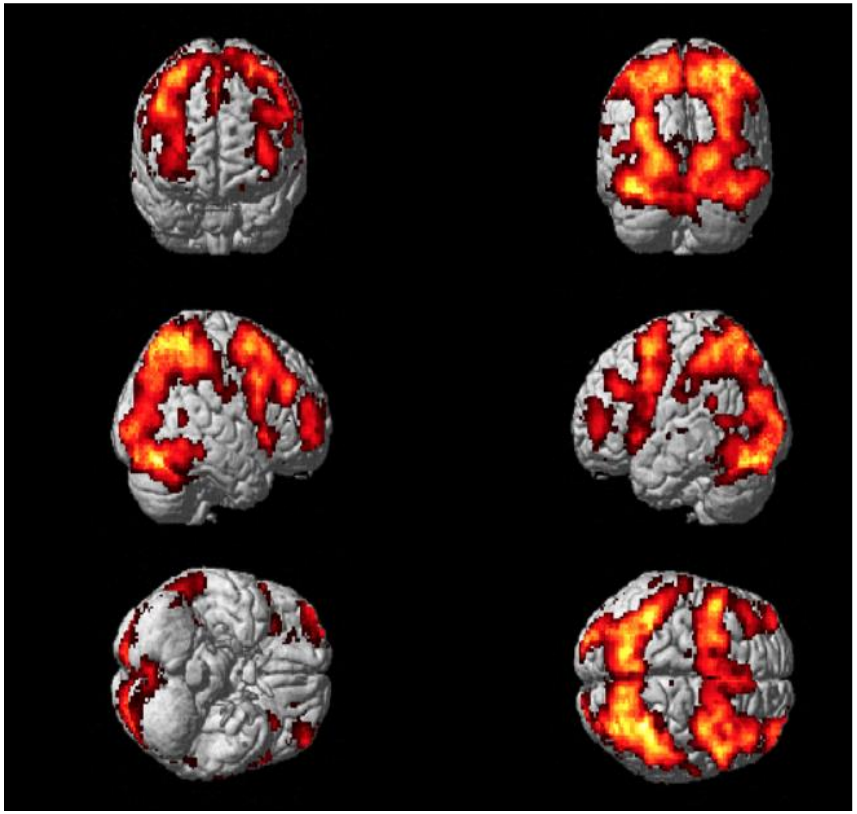
AGRICULTURE • INNOVATION • LIFE

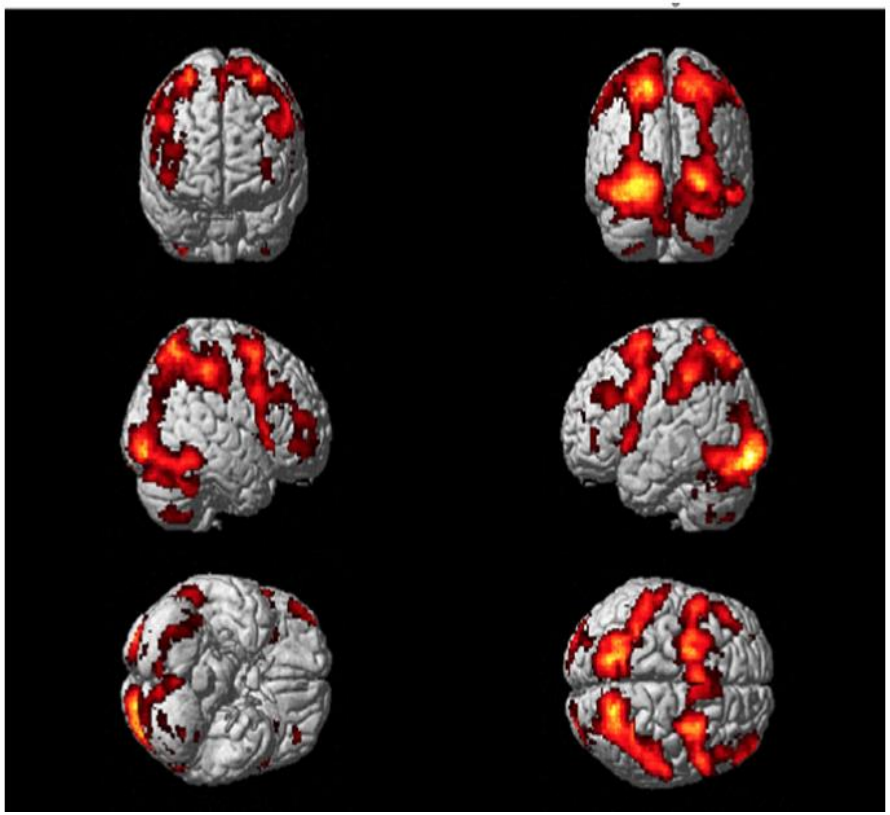



Statistical Parametric Mapping (SPM)
Montreal Neurological Institute (MNI)
Tailarach space

# fMRI – increased activation during working memory task







UPM-TUDM fMRI study . Submitted to JIMR 2018

# '$^{99m}$Tc-HMPAOSPECT imaging

- Utilizes hexamethylpropylene amine oxime (HMPAO) which is tagged to a metastabil radio-isotope Tc-99m,
- is taken up by brain tissue -> proportional to brain blood flow -> cerebral blood flow can be assessed
- Areas of low uptake will be interpreted as having reduced perfusion
- Classical pattern in AD is posterior hypoperfusion in the temporo-parietal lobes

# 18F-FDG PET/CT imaging

AGRICULTURE • INNOVATION • LIFE

ScienceDirect Journals & Bo

Outline Download Export

Radiation Physics and Chemistry

Volume 147, June 2018, Pages 35-39

## Reliability of standardized uptake value normalized to lean body mass using the liver as a reference organ, in contrast-enhanced 18F-FDG PET/CT imaging

Nur Hafizah Mohad Azmi [a, 1], Subapriya Suppiah [b, c, 1], Chang Wing Liong [b], Noramaliza Mohd Noor [c], Salmiah Md. Said [d], Muhammad Hafiz Hanafi [b], Chalermrat Kaewput [e], Fathinul Fikri Ahmad Saad [b, c], Sobhan Vinjamuri [f]

Show more

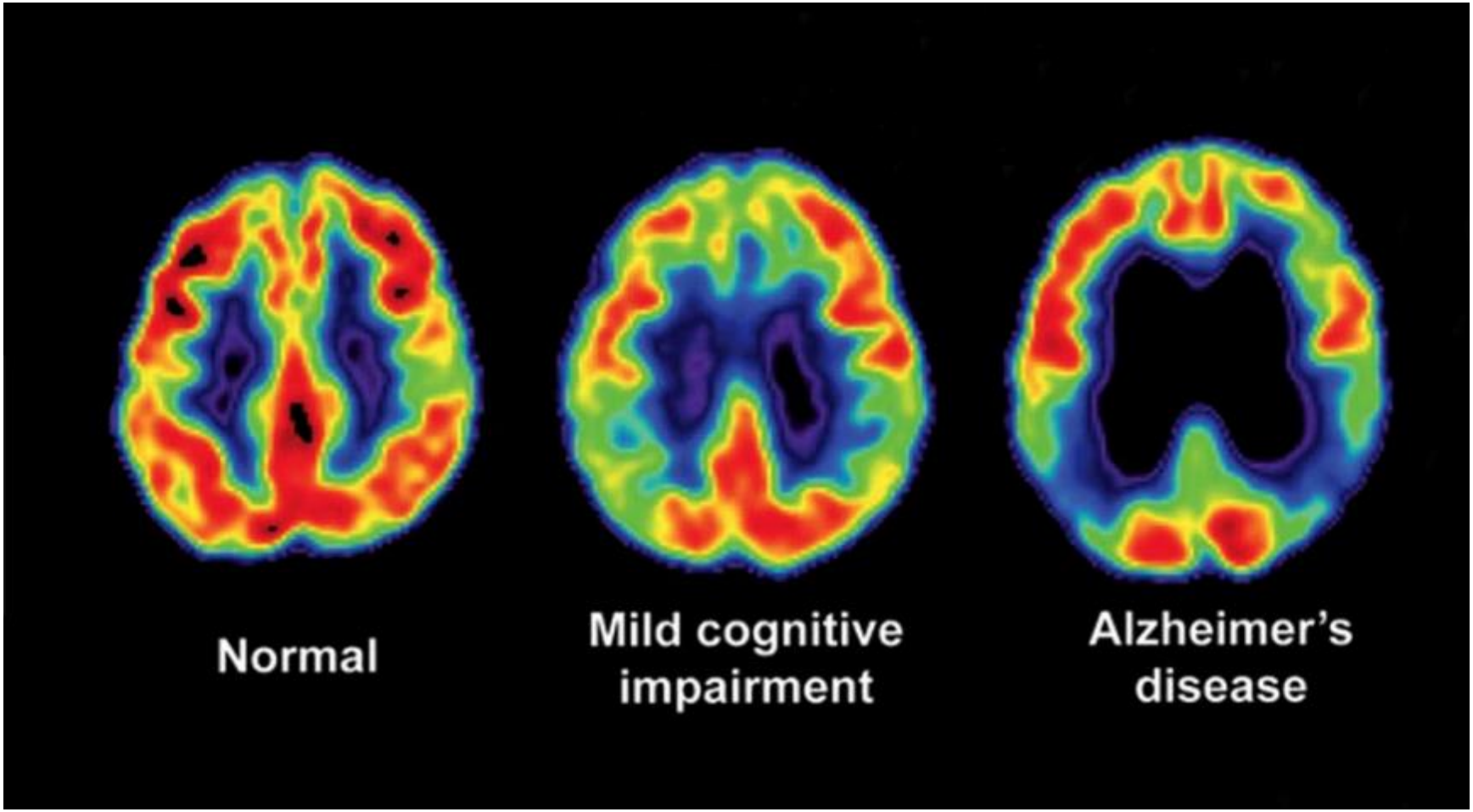
https://doi.org/10.1016/j.radphyschem.2018.01.019

Get rights and content

FDG uptake in cells can be quantified using SUV , SUL

# 18F-FDG PET/CT imaging

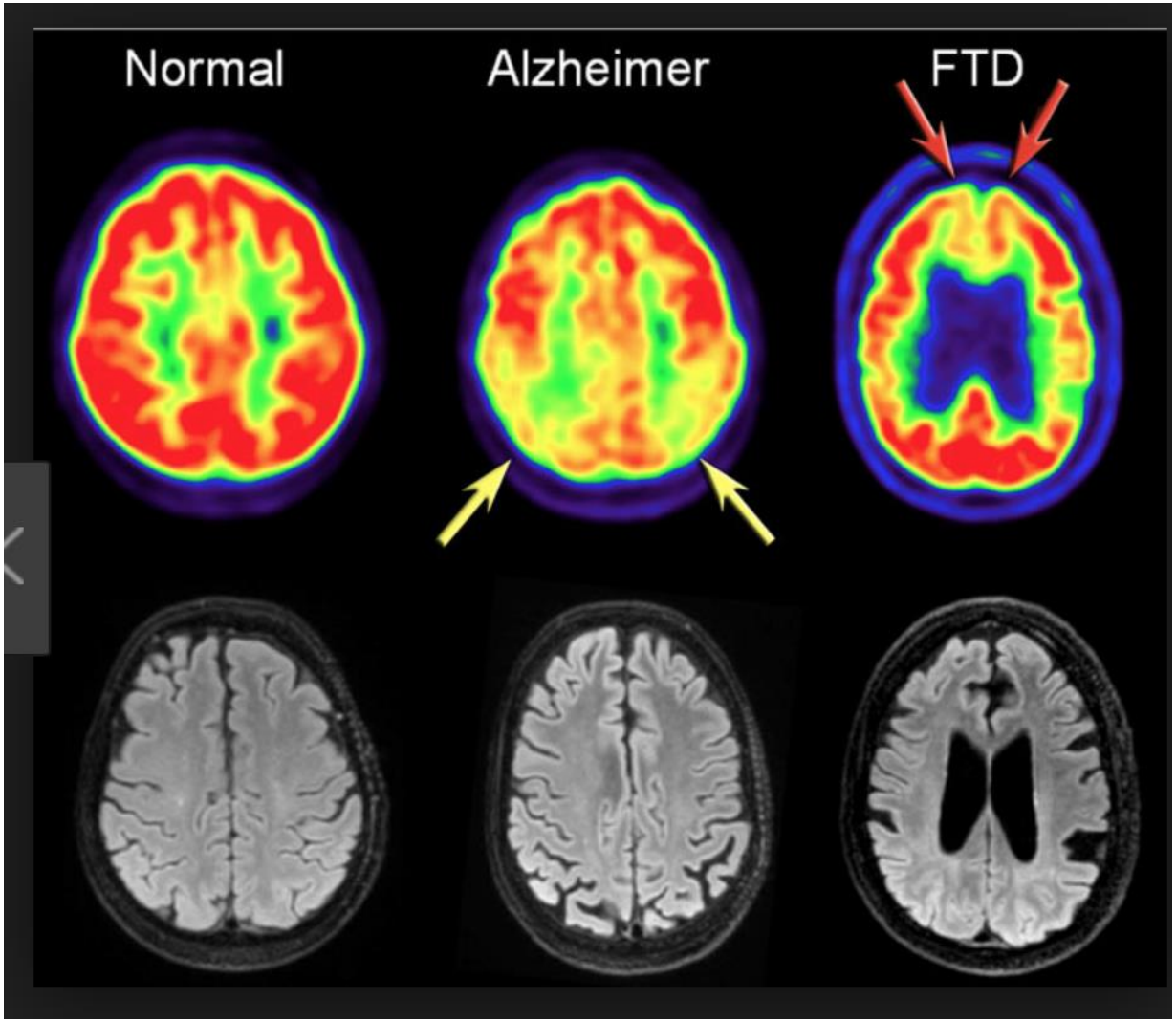




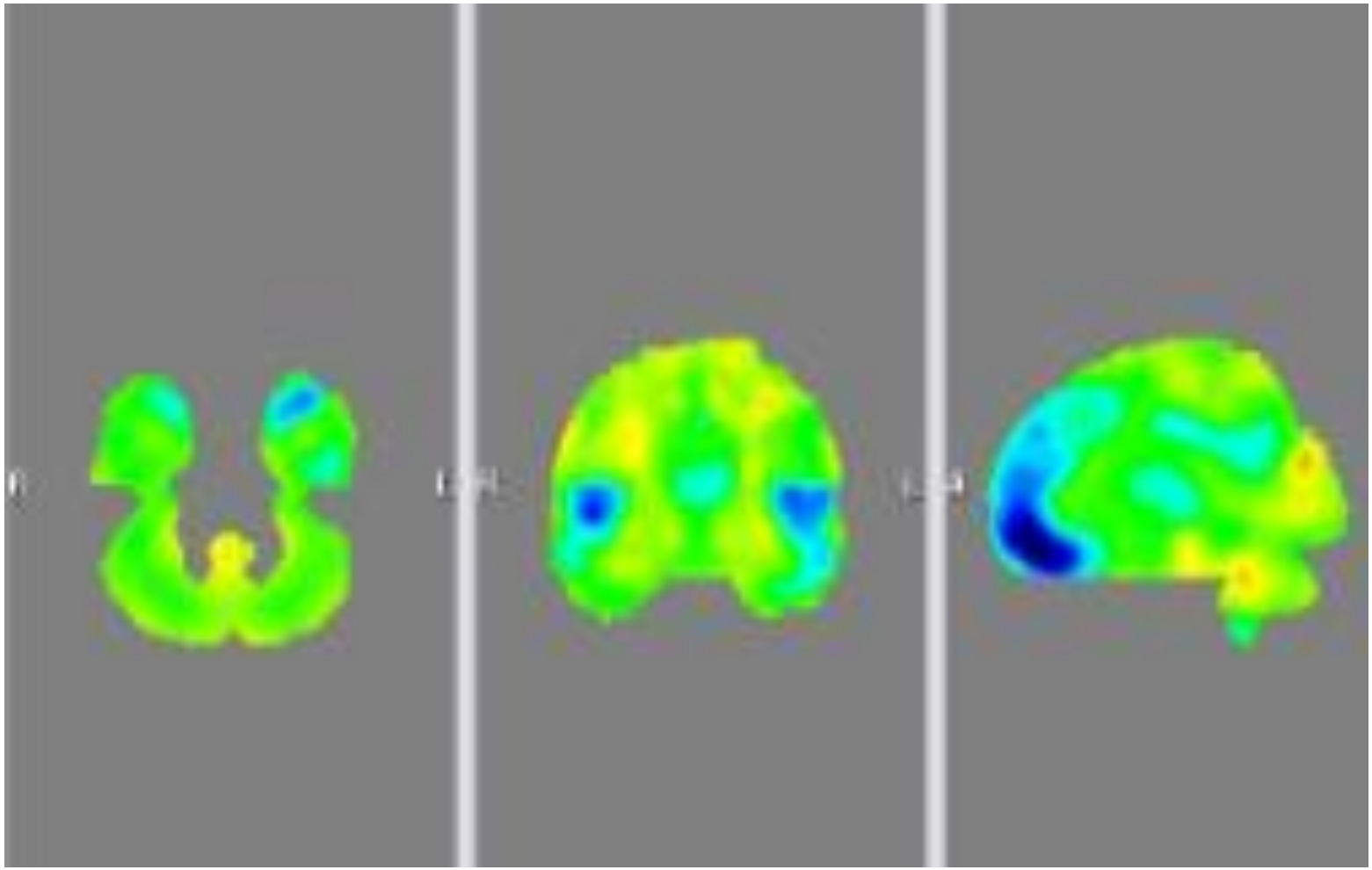

Neurology advisor

# 18F-FDG PET/CT imaging

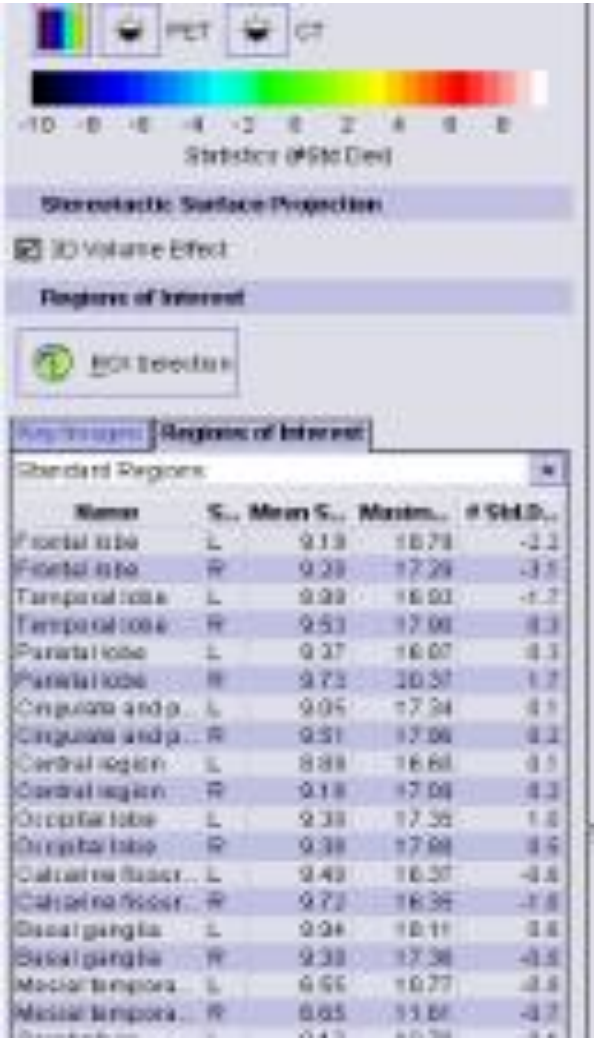


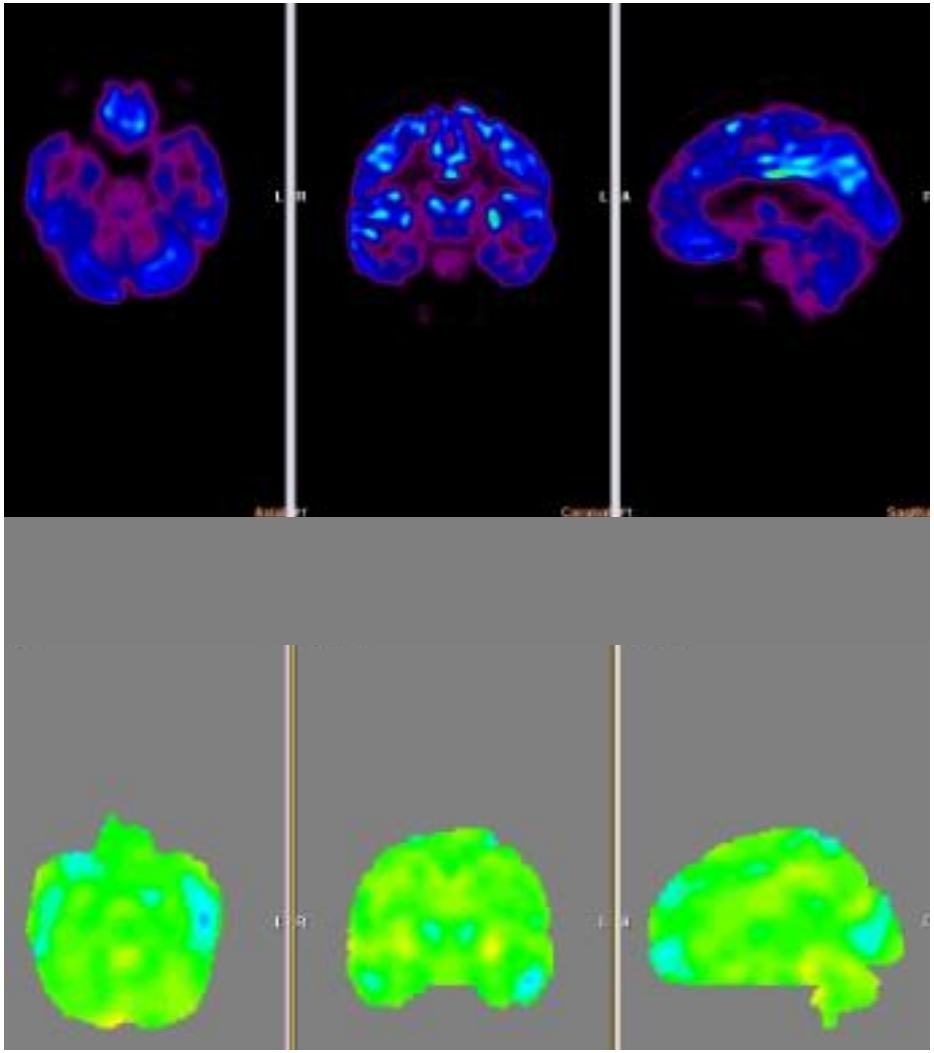


# 18F-FDG scan Positive Pattern for AD



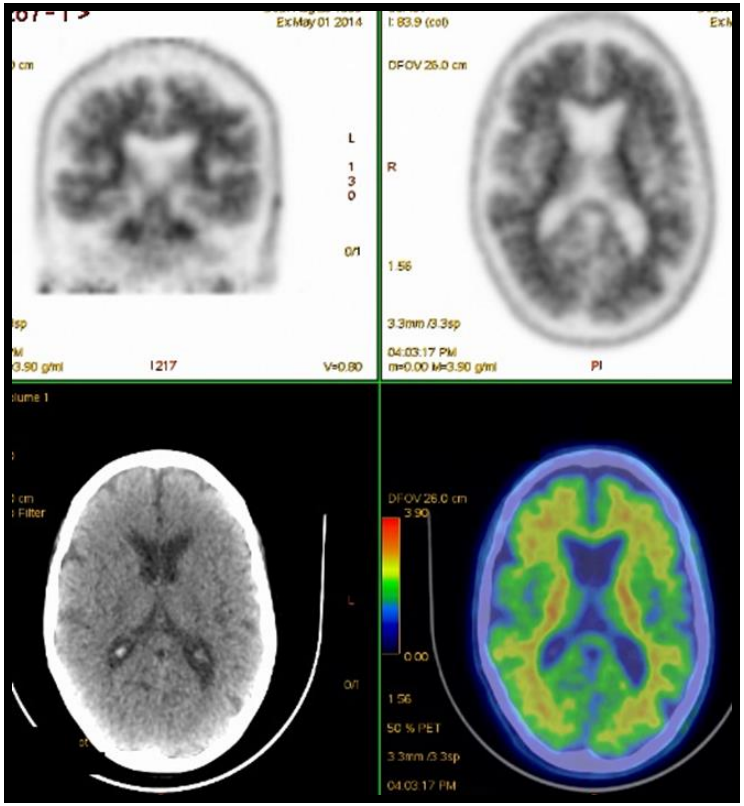
# 18F-FDG PET/CT BRAIN



# PET/CT Amyloid scan





- Good grey-white matter contrast indicates negative scan.
- Loss of grey-white matter contrast Indicates β amyloid plaque deposition, and in the correct clinical setting, it is suggestive of diagnosis of AD.
- Negative scan is inconsistent with diagnosis of AD

# Potential Prognostic Marker

AGRICULTURE • INNOVATION • LIFE

PLOS ONE | Publish | About | Browse | Search | advanced search

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Dissociation between Brain Amyloid Deposition and Metabolism in Early Mild Cognitive Impairment

Liyong Wu, Jared Rowley, Sara Mohades, Antoine Leuzy, Marina Tedeschi Dauar, Monica Shin, Vladimir Fonov, Jianping Jia, Serge Gauthier, Pedro Rosa-Neto, the Alzheimer's Disease Neuroimaging Initiative

Published: October 24, 2012 • http://dx.doi.org/10.1371/journal.pone.0047905

25 Save | 15 Citation | 4,602 View | 3 Share

Article | Authors | Metrics | Comments | Related Content

Download PDF | Print | Share

Abstract
Introduction
Materials and Methods
Results
Discussion
Author Contributions
References

Reader Comments (0)
Media Coverage (0)
Figures

Abstract

Background

The hypothetical model of dynamic biomarkers for Alzheimer's disease (AD) describes high amyloid deposition and hypometabolism at the mild cognitive impairment (MCI) stage. However, it remains unknown whether brain amyloidosis and hypometabolism follow the same trajectories in MCI individuals. We used the concept of early MCI (EMCI) and late MCI (LMCI) as defined by the Alzheimer's disease Neuroimaging Initiative (ADNI)-Go in order to compare the biomarker profile between EMCI and LMCI.

Objectives

To examine the global and voxel-based neocortical amyloid burden and metabolism among individuals who are cognitively normal (CN), as well as those with EMCI, LMCI and mild AD.

CrossMark

Subject Areas

Cognitive impairment
Alzheimer disease
Magnetic resonance...
Positron emission to...
Memory
Biomarkers
Recall (memory)

Wu et al (2012) PLOS One Online Journal : PET/CT Amyloid scans are positive even in subjects having early MCI. It may be a useful imaging tool for early detection of AD.

# Quantification of brain amyloid burden


European Journal of Nuclear Medicine and Molecular Imaging
April 2012, Volume 39, Issue 4, pp 621–631

## Using PET with $^{18}$F-AV-45 (florbetapir) to quantify brain amyloid load in a clinical environment

V. Camus, P. Payoux, L. Barré, B. Desgranges, T. Voisin, C. Tauber, R. La Joie, M. Tafani, C. Hommet, G. Chételat, K. Mondon, V. de La Sayette, J. P. Cottier, E. Beaufils, M. J. Ribeiro ... show 6 more

Open Access | Original Article
**First Online:** 18 January 2012
**DOI**: 10.1007/s00259-011-2021-8

**Cite this article as:**
Camus, V., Payoux, P., Barré, L. et al.
Eur J Nucl Med Mol Imaging (2012) 39: 621. doi:10.1007/s00259-011-2021-8



### Abstract

#### Purpose

Positron emission tomography (PET) imaging of brain amyloid load has been suggested as a core biomarker for Alzheimer's disease (AD). The aim of this study was to test the feasibility of using PET imaging with $^{18}$F-AV-45 (florbetapir) in a routine clinical environment to differentiate between patients with mild to moderate AD and mild cognitive impairment (MCI) from normal healthy controls (HC).

#### Methods

Camus et al (2012) Eur J of Nuc Med and Mol Imaging: 18F- Florbetapir is a safe biomarker to quantify brain amyloid load; but suggest for better automatic or semiautomatic quantification to improve specificity

ORIGINAL ARTICLE

# The role of PET/CT amyloid Imaging compared with Tc99m-HMPAO SPECT imaging for diagnosing Alzheimer's disease

**Subapriya Suppiah, MRAD[1,2], Siew Mooi Ching, MFamMed[1], Abdul Jalil Nordin, MRad[2], Sobhan Vinjamuri, FRCP[3]**

[1]Department of Family Medicine, Faculty of Medicine,Universiti Putra Malaysia, Serdang, Malaysia. [2]Centre for Diagnostic Nuclear Imaging, Faculty of Medicine,Universiti Putra Malaysia, Serdang, Malaysia. [3]Royal Liverpool University Hospital, Liverpool, United Kingdom.

**ABSTRACT**

**Background: Imaging such as Tc99m-HMPAO single photon emission computed tomography (SPECT), and positron emission tomography/ computed tomography (PET/CT) amyloid scans are used to aid the diagnosis of Alzheimer's disease (AD).**

**Objective: We aimed to correlate the ability of these modalities to differentiate Probable AD and Possible AD using the clinical diagnosis as a gold standard. We also**

**INTRODUCTION**

According to the Diagnostic and Statistics Manual of Mental Disorders 5th Edition (DSM-5) criteria, Alzheimer's disease (AD) is now termed as a major neurocognitive disorder (NCD). NCD, previously known with the term dementia, is a clinical spectrum that involves a progressive decline in cognitive function and is evidenced by reduced performance in a neuropsychiatric test in the absence of other mental illness or medical conditions. It is also associated with significant impairment in the ability to independently

Suppiah et al (2018) Medical Journal of Malaysia Med J Malaysia Vol 73 No 3 June 2018 ; 148-152 .

Conclusion: detection of Aβ plaques is not diagnostic of AD, negative scans are inconsistent with the diagnosis of AD, thus efforts need to be intensified to find non-AD cause of the neurocognitive deficit.

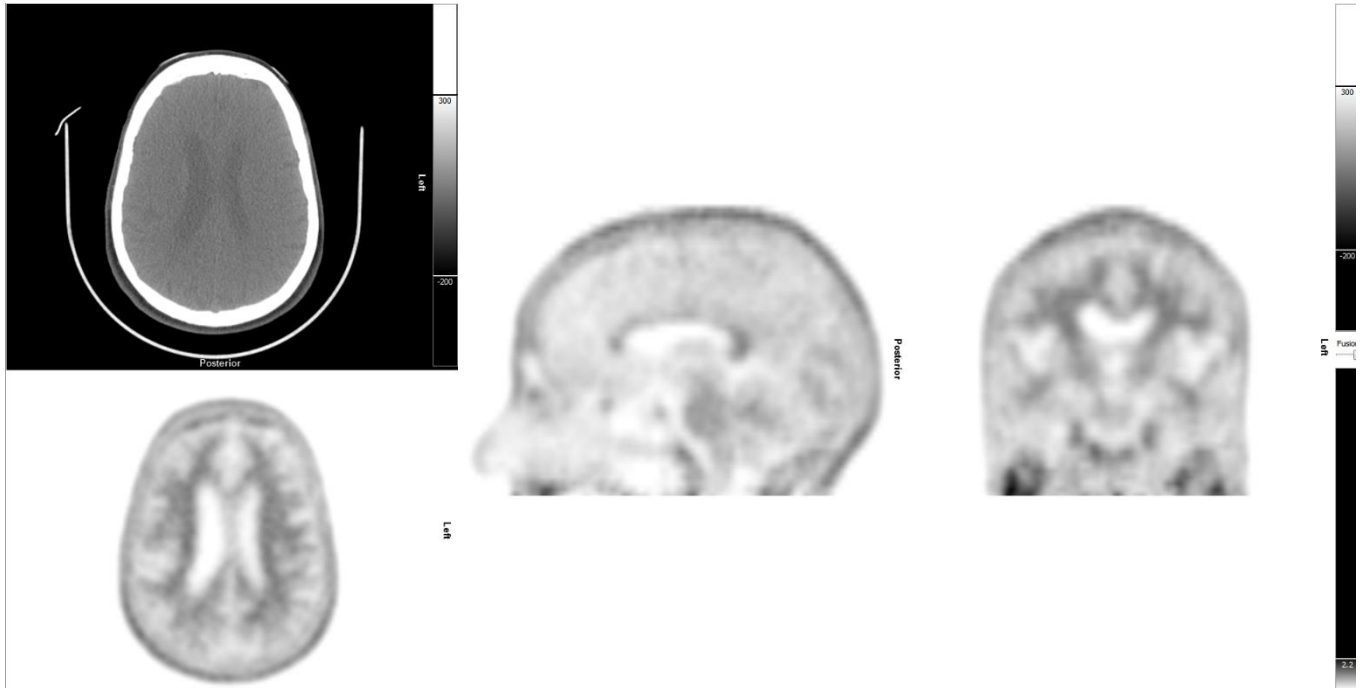
# Results

AGRICULTURE • INNOVATION • LIFE

| Modality | MRI | Tc99m_HMPAO SPECT | SPECT & PET Combo Reading | Amyloid PET/CT |
|---|---|---|---|---|
| Sample size (n) | 22 | 27 | 27 | 47 |
| Sensitivity (95% CI) | 66.7% (24.1 – 94.0) | 87.5% (46.7 – 99.3) | 87.5% (46.7 – 99.3) | 62.5% (35.9 – 83.7) |
| Specificity (95% CI) | 56.3% (30.6 – 79.2) | 73.7% (48.6 – 89.9) | 84.2% (59.5 – 95.8) | 77.4% (58.5 – 89.7) |
| PPV (95% CI) | 36.4% (12.4 – 68.4) | 58.3% (28.1 – 83.5) | 70.0% (35.4 – 91.9) | 58.8% (33.5 – 80.6) |
| NPV (95% CI) | 81.8% (47.8 – 96.8) | 93.3% (66.0 – 99.7) | 30.0% (8.1 – 64.6) | 80.0% (60.9 – 91.6) |
| Pearson's correlation (p value) | 0.437 | 0.014 | 0.002 | 0.007 |

# Negative Amyloid Scan

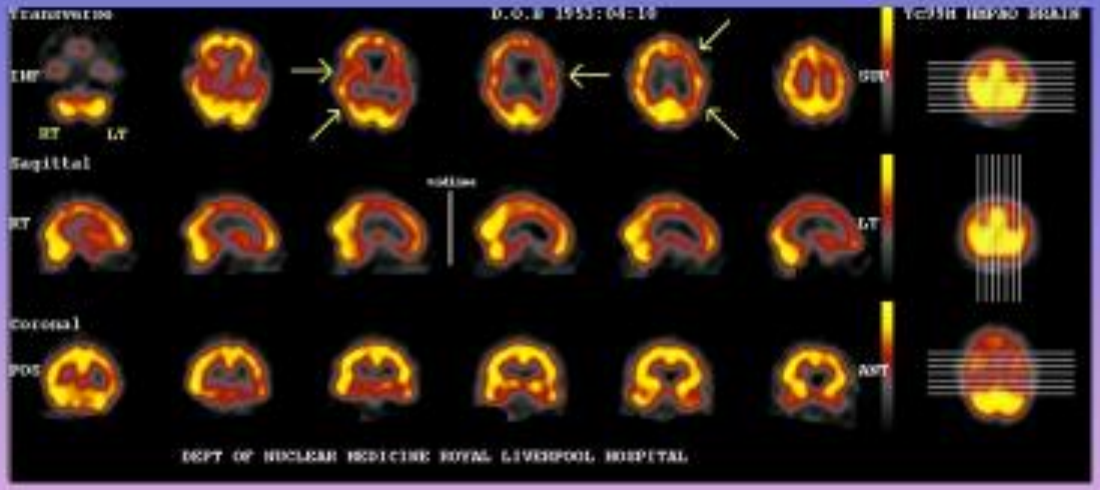


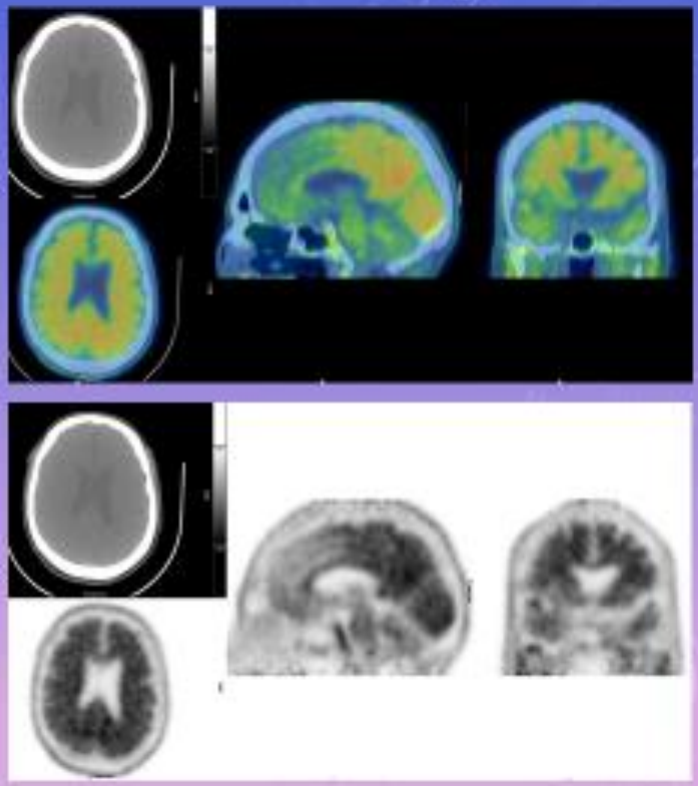


# Compatible with diagnosis of AD



## CLASSICAL AD

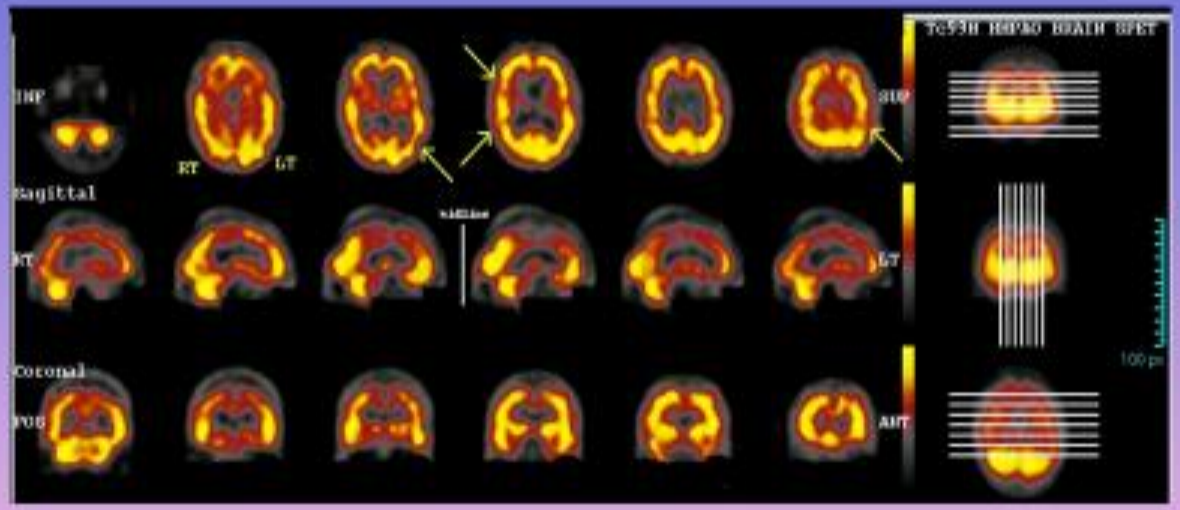


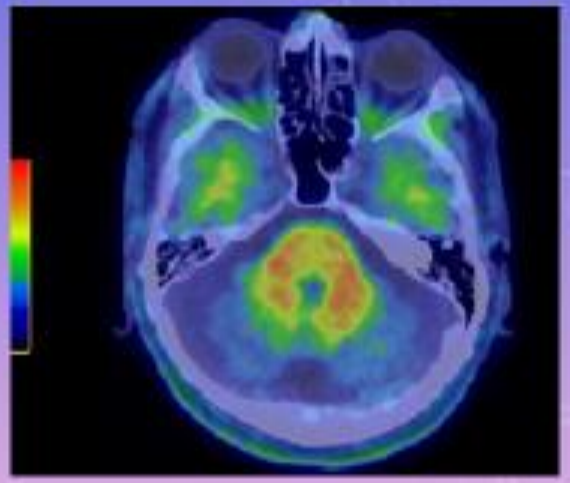
# Inconsistent with Dx of AD

AGRICULTURE • INNOVATION • LIFE

## VASCULAR DEMENTIA




Multiple foci of focal hypoperfusion on Tc99m-HMPAO SPECT imaging

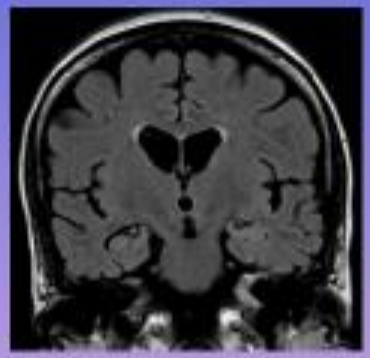


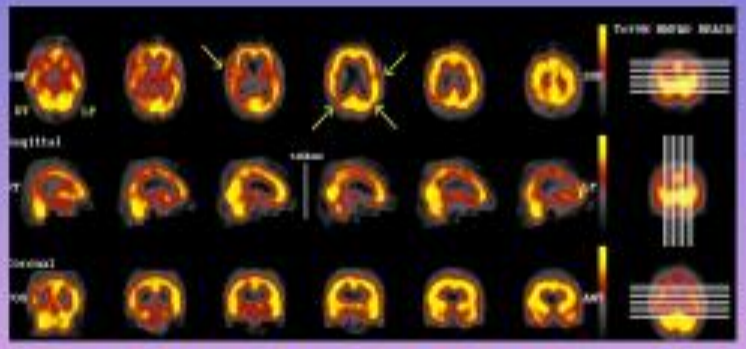
Normal PET/CT Amyloid scan

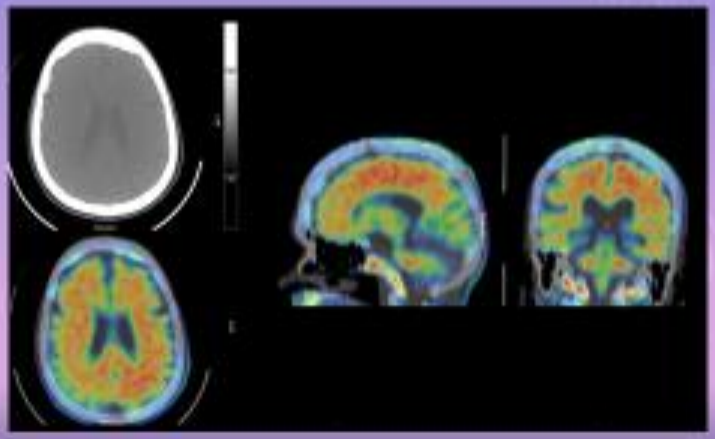
# Multimodality Imaging

AGRICULTURE • INNOVATION • LIFE

## AD: CORRELATION WITH MRI, SPECT & PET/CT







## Florbetapir F18 Scan Usage: Information Summary.

A negative florbetapir scan:

- indicates sparse to no neuritic plaques.
- is inconsistent with a neuropathological diagnosis of Alzheimer's disease at the time of image acquisition.
- reduces the likelihood that a patient's cognitive impairment is due to Alzheimer's disease.

A positive florbetapir scan:

- indicates moderate to frequent amyloid neuritic plaques.
- may be observed in older people with normal cognition and in patients with various neurologic conditions, including Alzheimer's disease.

Important florbetapir scan limitations:

- A positive scan does not establish a diagnosis of Alzheimer's disease or other cognitive disorder.
- The scan has not been shown to be useful in predicting the development of dementia or any other neurologic condition, nor has usefulness been shown for monitoring responses to therapies.

Yang, L et al. (2012) Brain Amyloid Imaging — FDA Approval of Florbetapir F18 Injection, New England Journal of Medicine, 367(10); 885-887

# Clinical indications for amyloid scan



1. Patients with persistent / progressive unexplained MCI
2. Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation (atypical clinical course /etiologically mixed presentation)
3. Patients with progressive NCD and atypically early age of onset (usually defined as 65 years or less in age)

Amyloid imaging is inappropriate in the following situations: 4. Patients with core clinical criteria for probable AD with typical age of onset

5. To determine dementia severity
6. Based solely on a positive family history of dementia or presence of apolipoprotein E (APOE)ε4
7. Patients with a cognitive complaint that is not confirmed on clinical examination
8. In lieu of genotyping for suspected autosomal mutation carriers
9. In asymptomatic individuals
10. Nonmedical use (e.g., legal, insurance coverage, or employment screening)

Johnson et al. (2013) Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association, Alzheimer's & Dementia; 9: e1–e16

# Conclusion

AGRICULTURE • INNOVATION • LIFE

The addition of molecular imaging for brain imaging in patients with atypical symptoms of neurocognitive disorders can aid in diagnosis of Alzheimer's disease by improving diagnostic confidence and provide justification for commencement of appropriate treatment. Potential to act as a baseline scan to assess response to treatment.

# PUSAT PENGIMEJAN DIAGNOSTIK NUKLEAR (PPDN) UPM

AGRICULTURE • INNOVATION • LIFE

# Postgraduate studies at PPDN UPM

AGRICULTURE • INNOVATION • LIFE

Computer and Embedded Systems Engineering
Computer Networks
Control System Engineering
Electrical Power Engineering
Electronic Engineering
Environmental Engineering
Farm Structures
Food Engineering
Geographic Information System
Geospatial Engineering

Remote Sens
Safety, Healt
Sensor Techn
Signal Proces
Soil and Wate
Structural En
Water Resou
Wireless Con
Engineering

**FACULTY OF ENVIRONMENTAL STUD**

Environmental Education and Ethics
Environmental Hydrology and Hydrogeology
Environmental Economics, Planning and Management
Environmental Policy and Governance

Environmenta
Environmenta
Environmenta
Marine and Freshwater Ecosystem

**FACULTY OF MEDICINE AND HEALTH SCIENCES**

Applied Physics
Biochemistry
Bioinformatics and System Biology
Cancer Biology and Oncology
Chemical Pathology
Clinical Nutrition
Community Nutrition
Environmental Health
Epidemiology and Biostatistics
Forensic Science
Hematology
Health Education and Communication
Health Promotion
Health Service Management
Human Anatomy
Human Genetics
Human Physiology
Immunobiology
Immunopharmacology
Materials Science
Medical Microbiology
Medical Parasitology
Medical Sciences
Microbial Biotechnology
Molecular Biology and Genetic Engineering
Molecular Biotechnology
Molecular Imaging
Molecular Medicine
Neuroscience
Nursing
Nutritional Sciences
Occupational Safety and Health
Pharmacology and Toxicology
Psychological Medicine
Public Health
Radiology and Imaging
Safety, Health And Emergency Management
Social Gerontology
Stem Cell
Structural Biology
Youth Studies

**INSTITUTE FOR MATHEMATICAL RESEARCH**

http://www.eng.upm.edu.my/dokumen/SKPSI1_brosur_INTERNATIONAL.pdf

# Acknowledgement

Images are courtesy of the

- Centre for Diagnostic Nuclear Imaging (Pusat Pengimejan Diagnostik Nuklear- **PPDN**), UPM, Malaysia
- Department of NUCLEAR MEDICINE, Royal Liverpool and Broadgreen University Hospitals, NHS Trusts, Liverpool, UK – **RLBUHT,UK**

UNIVERSITI PUTRA MALAYSIA
BERILMU BERBAKTI

**TERIMA KASIH/*THANK YOU***

www.upm.edu.my