Neuroimaging Biomarkers in Alzheimer's disease

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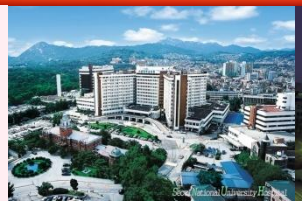


Contents

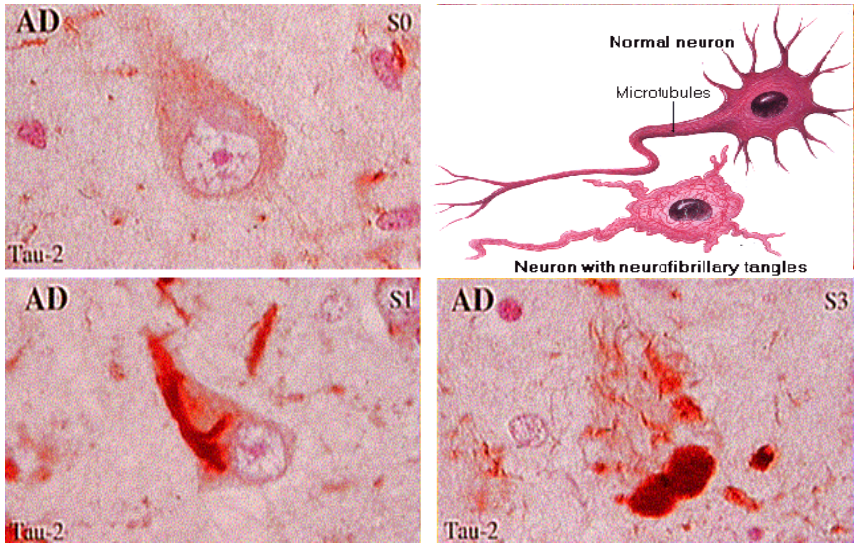
- Advantage of neuroimaging as a biomarker for AD
- What AD neuroimaging biomarkers reflect
- Application of neuroimaging biomarkers for AD

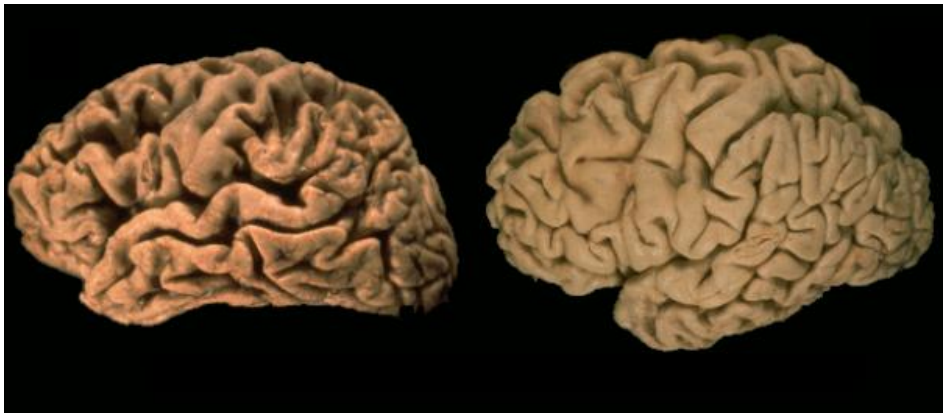
Alzheimer's Disease

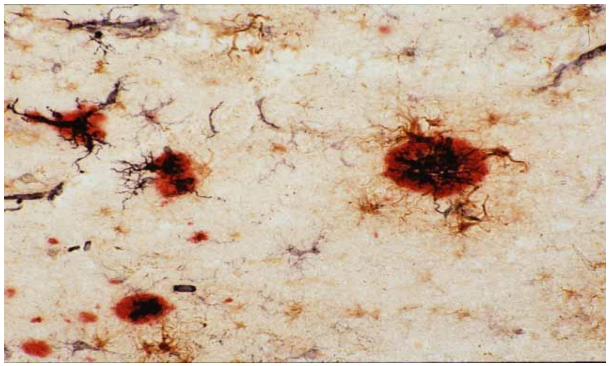
AD Imaging

- M/C causes of dementia
- Clinically, progressive memory & other cognitive decline, and various behavioral disturbances
- Neuropathologically, characteristic findings in brain

Neurofibrillary tangles
(intraneuronal change)







Senile (or neuritic) plaque
(extraneuronal change)

Advantage of Neuroimaging as a Biomarker for AD

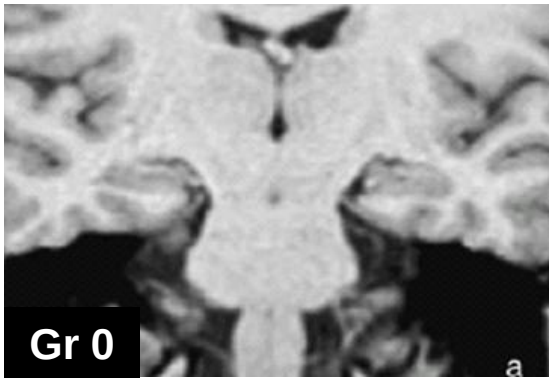
- Obtains information directly from the brain
- Much higher test-retest reliability
  : ICC > 0.95 for hippocampus volume measuring
- Has high “face validity” as an index of disease progression
- To some extent, have been quantitatively validated by correlation with cognition/function, and correlation with neuropathology

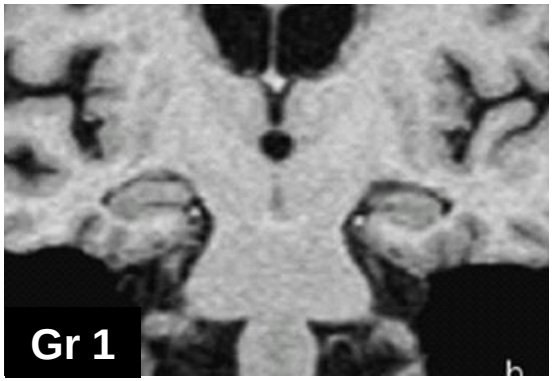
Neuroimaging Biomarkers in AD

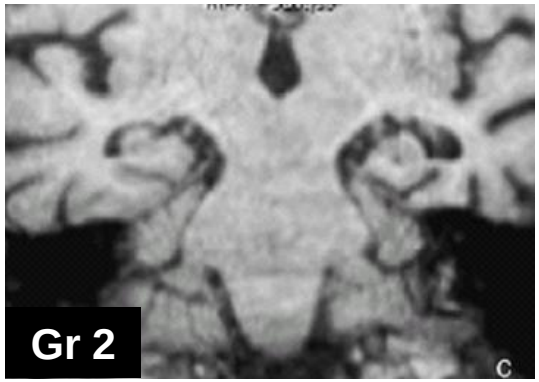
- Structural Neuroimaging (**MRI, DTI**)
- Functional Neuroimaging (**FDG-PET**)
- Molecular Neuroimaging (**amyloid PET**)

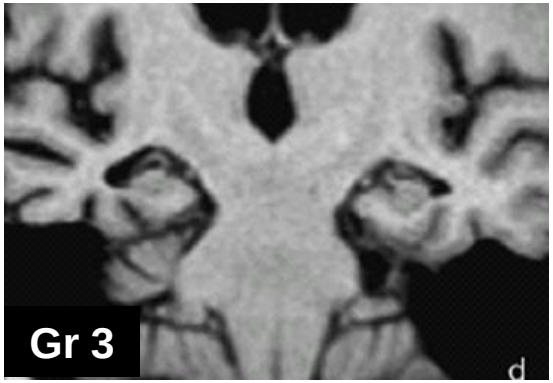
MTA on MRI

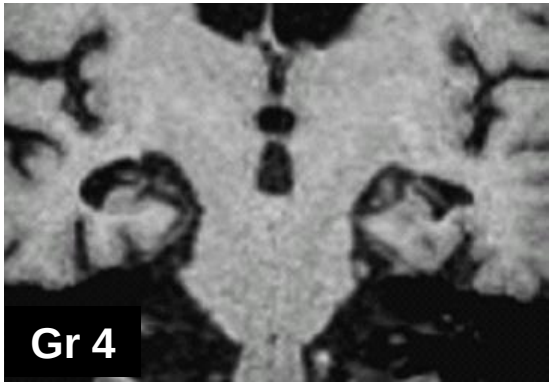
Medical Temporal Atrophy (MTA): the earliest finding in AD process





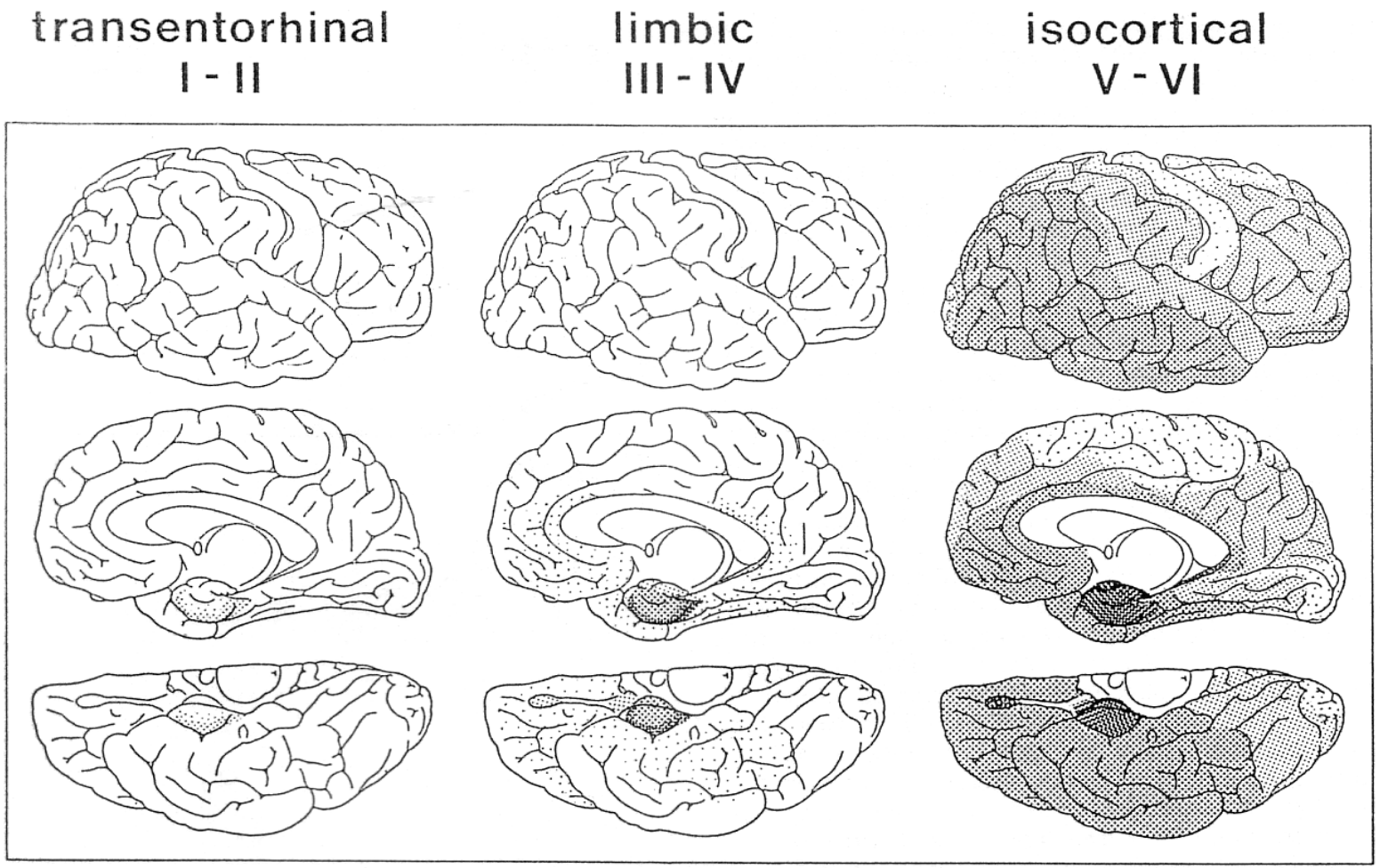




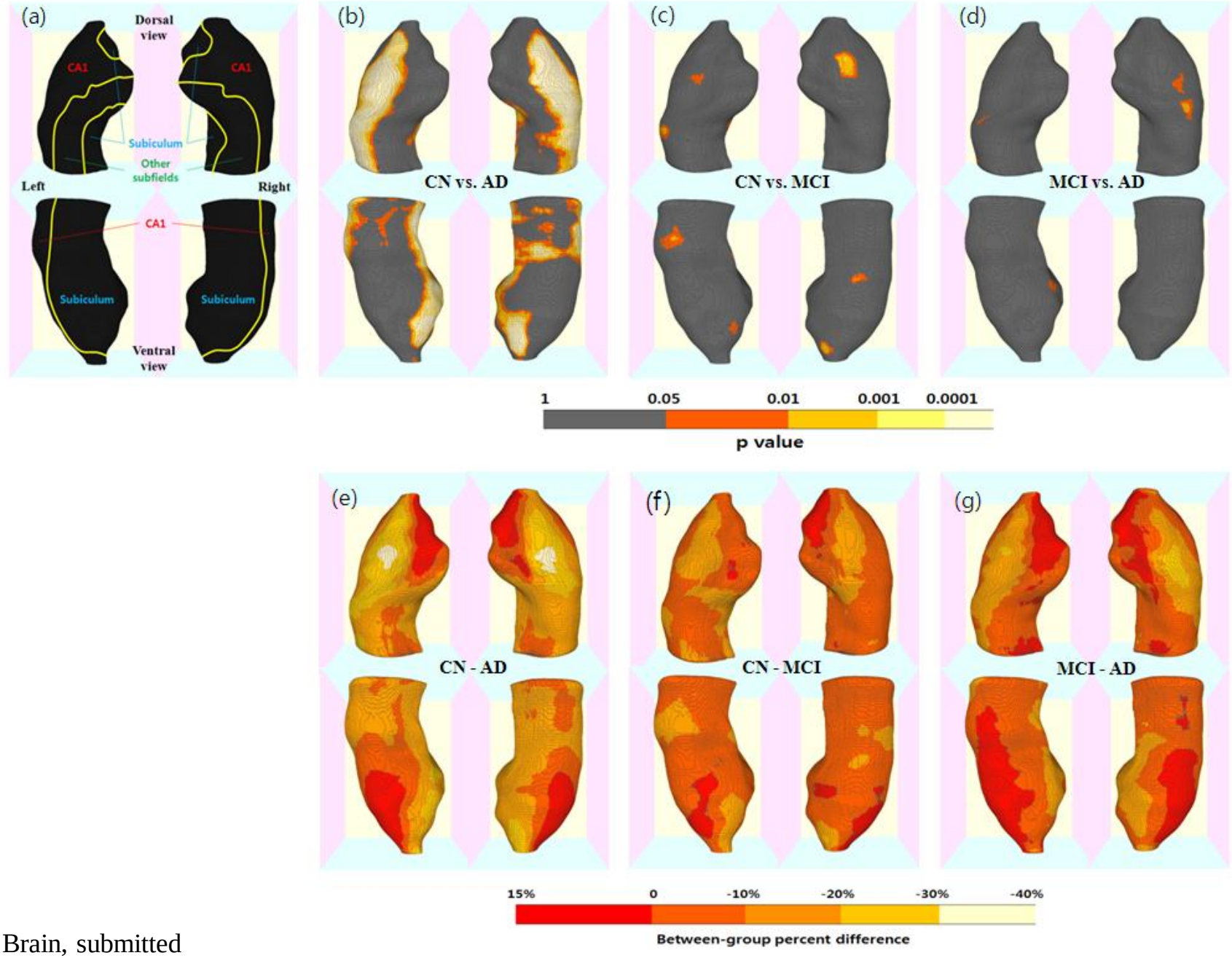


Scheltens (1992) JNNP

Evolution of NF change in AD



Braak & Braak. Acta Neuropathol 1991



Lee et al Brain, submitted

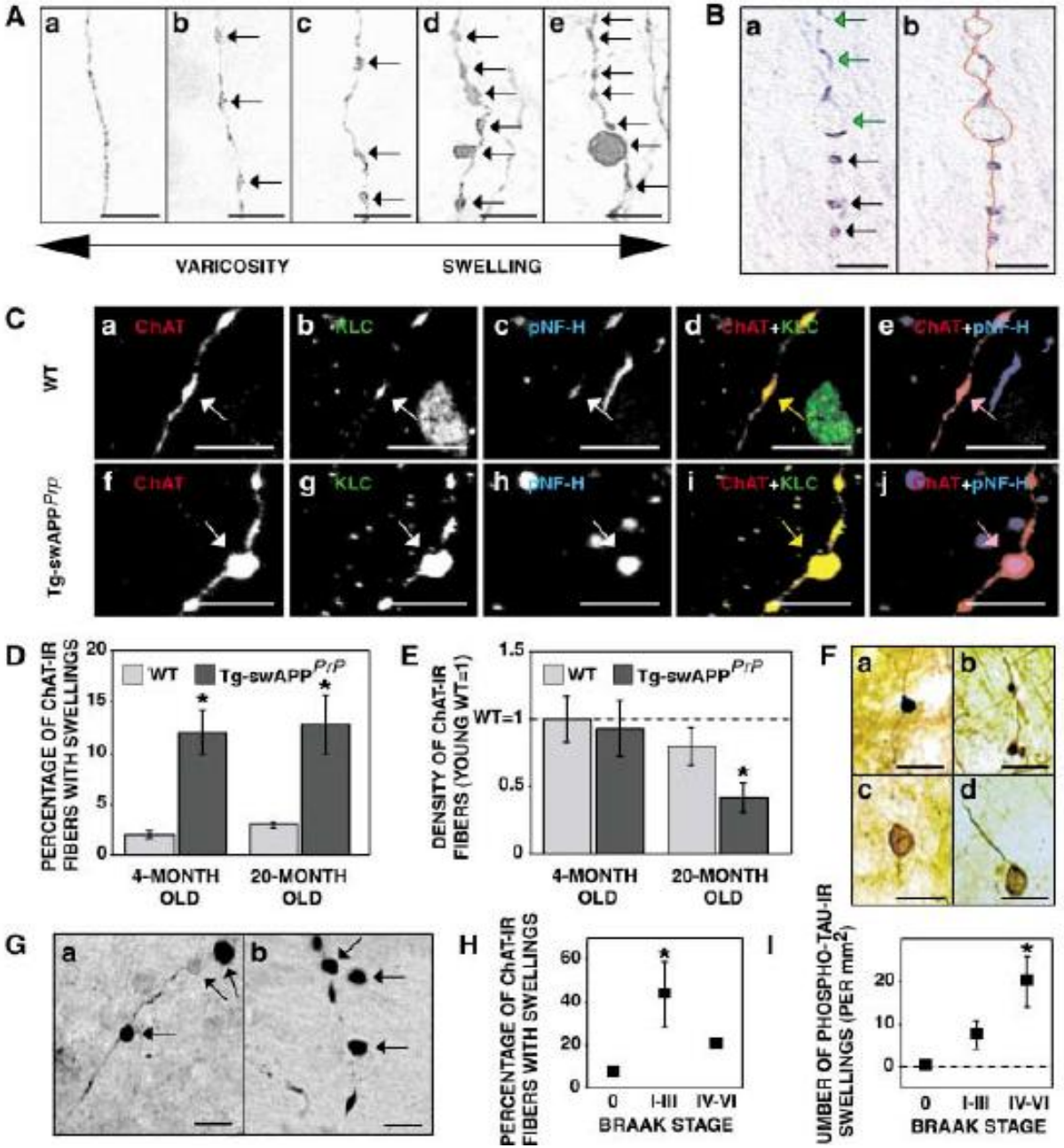
Regional hippocampal neuronal loss in AD indicated by neuropathological studies

Table 1
Summary of selected neuropathological studies (mostly using unbiased stereological methods) that quantified regional hippocampal neuronal density or number in Alzheimer's disease

	Controls, *N* (age)	Cases, *N* (age)	CA1	CA2	CA3	CA4	Subiculum	Pre-subiculum	Pro-subiculum	Hilus	Granule cell layer	Fascia dentata	Dentate gyrus	Age?[a]	Gender?	
Bobinski et al. (1998)		16 (?)	↓	↔	↔	↔	↓						↔	Y*	Y*	Among cases, # neurons, volume correlated with severity or duration of AD; *Controls for age and gender
Davies et al. (1983)	12 (54)	18 (74)	↓	↔	↔	↑	↓	↔	↓					N	N	Pyramidal neuron density
Giannakopoulos et al. (1996)	13 (99)	22 (98)	↔	↔			↔			↔				Y	N	Neuronal density; Also no difference very mild cognitive impairment group vs. controls
Kril et al. (2002)	7 (75)	5 (76)	↓	↓		↔	↓	↓					↔	Y	Y	Volume
Price et al. (2001)	14 (75)	17 (82)	↓											N	?	Number of neurons; mild or severe AD vs. controls. No difference preclinical vs. controls
Rossler et al. (2002)		28 (78)	↓	↔		↔	↓							N	N	Number of neurons; AD Stage V vs. AD Stage I
Simic et al. (1997)	10 (80)	13 (84)	↔	↔			↓			↔	↓	↔		Y	Y	Number of neurons
von Gunten et al. (2005)	6 (95)	6 (96)	↓	↓									↓	Y	Y	Number of neurons; CDR 0–0.5 vs. CDR 1–2
West et al. (1994)	14 (78)	7 (79)	↓	↔			↓			↓	↔			Y	?	Number of neurons
West et al. (2004)	11 (82)	14 (82)	↓	↔			↔			↔	↔			Y	Y	Number of neurons; AD vs. controls; no differences preclinical AD vs. controls; data shown for men only
Zarow et al. (2005)	6 (82)	9 (83)	↓	↓										Y	N	Number of neurons

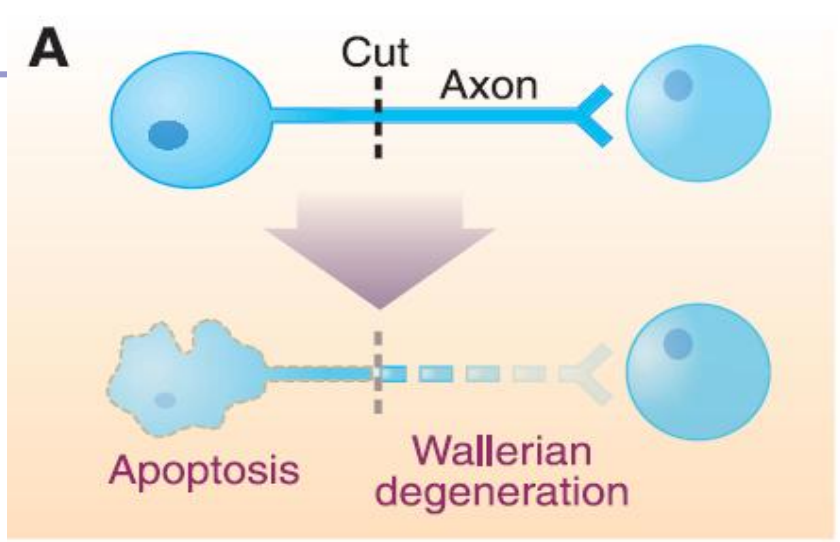
↓: Smaller in cases than controls.
↔: No difference between cases and controls.
↑: Larger in cases than controls.
CDR: Clinical Dementia Rating Scale.
[a] Are cases and controls similar by age, gender?

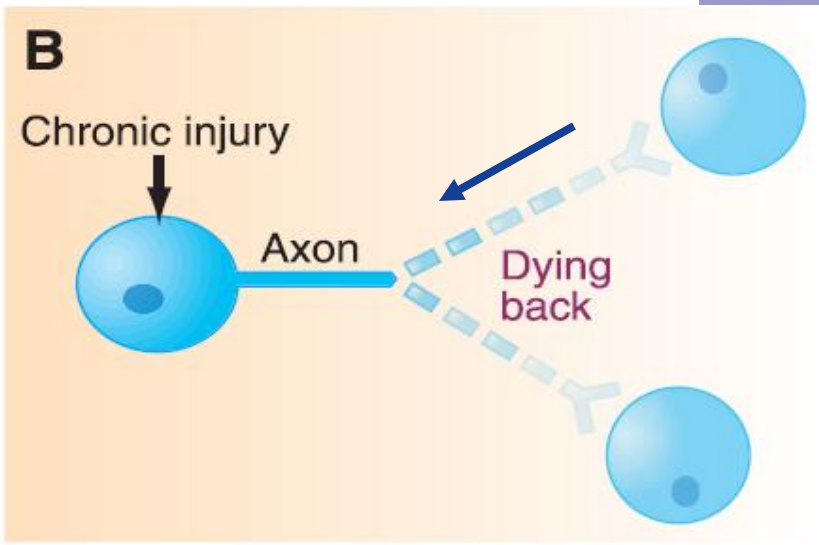
axonal defects in mouse models (A~F) and in human AD (G~I)



Stokin et al. Science 2005

Mechanism of WM injury in AD





PNS & CNS
Trauma, vascular accident, infection, or immune response locally injures axons

Very quick (<1~2days) in PNS, but much slower in CNS

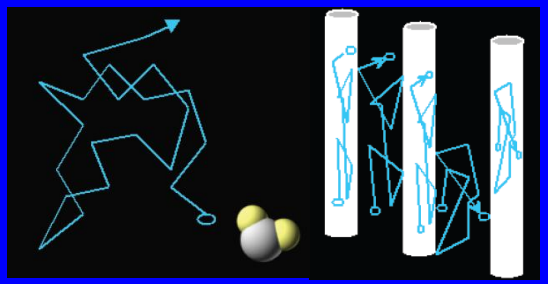
PNS
Polyneuropathies ass with diabetes, alcoholism, arylamide poisoning, AIDS
CNS
Neurogenerative disease, including MND, **AD** and PD

Over weeks or months in both PNS and CNS

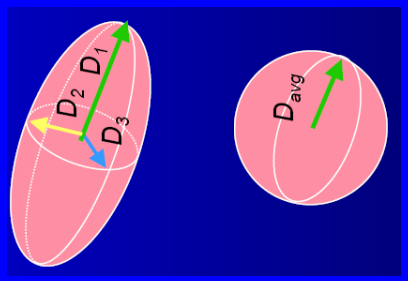
Raff et al. Science 2002; Coleman. Nat Rev Neurosci 2005

Diffusion tensor imaging (DTI) basic

AD Imaging

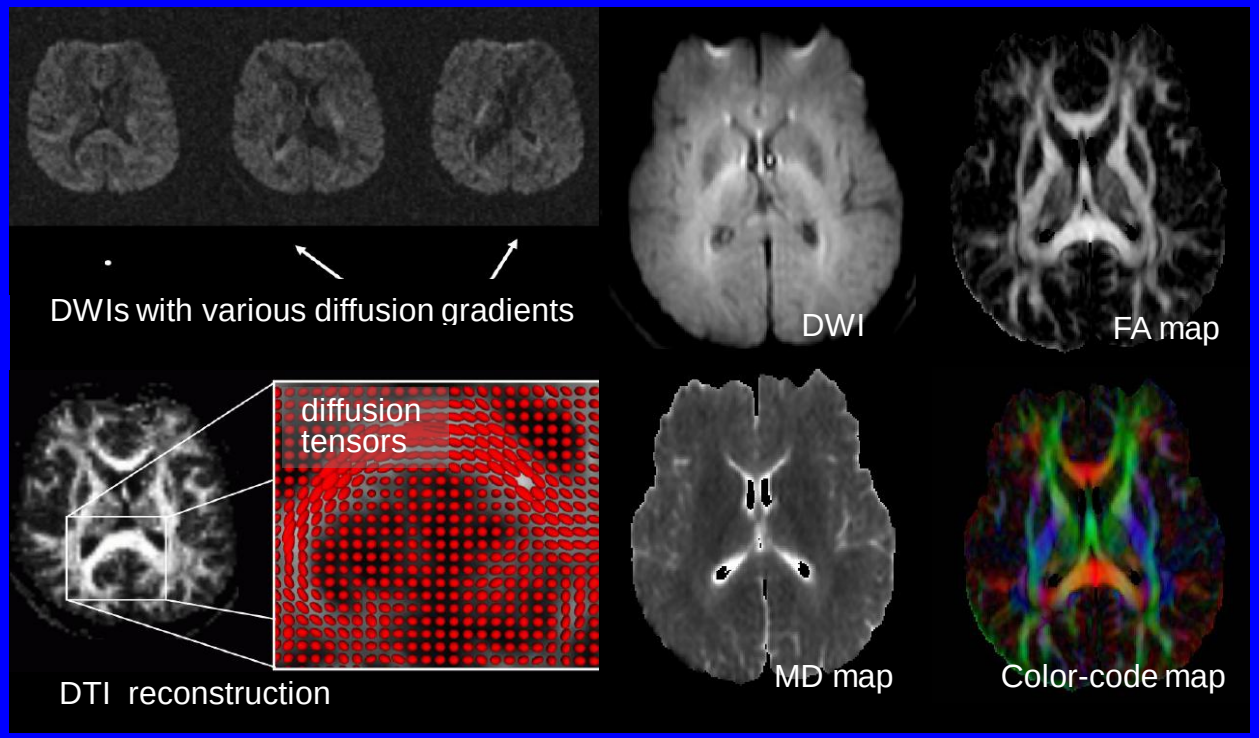


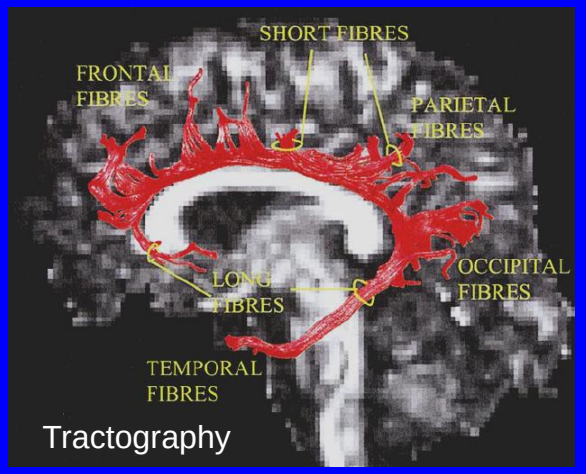
Water diffusion Oriented fibers



FA **MD**

- FA (fractional anisotropy): WM integrity measure
- MD (mean diffusivity): measure for randomized mean water diffusion (=ADC)

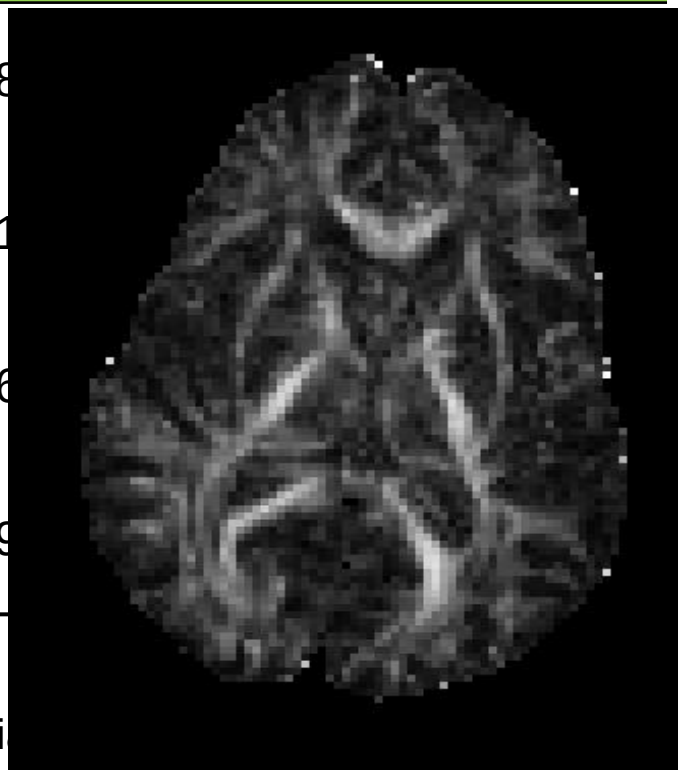




Group comparisons of mean FA for baseline anisotropy level-stratified ROIs

AD Imaging

	CN	MCI	AD	P value
H1 WM FA	0.619 ± 0.061	0.606 ± 0.058		
H2 WM FA	0.479 ± 0.042	0.471 ± 0.041		
H3 WM FA	0.386 ± 0.032	0.378 ± 0.036		
H4 WM FA	0.308 ± 0.023	0.304 ± 0.029		



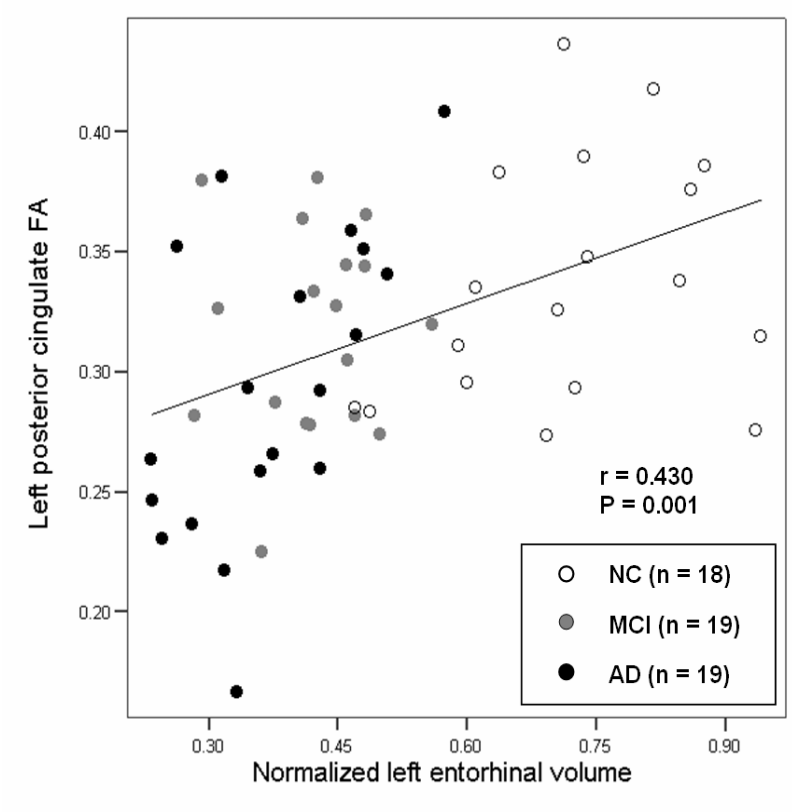
Data presented as means ± SD.

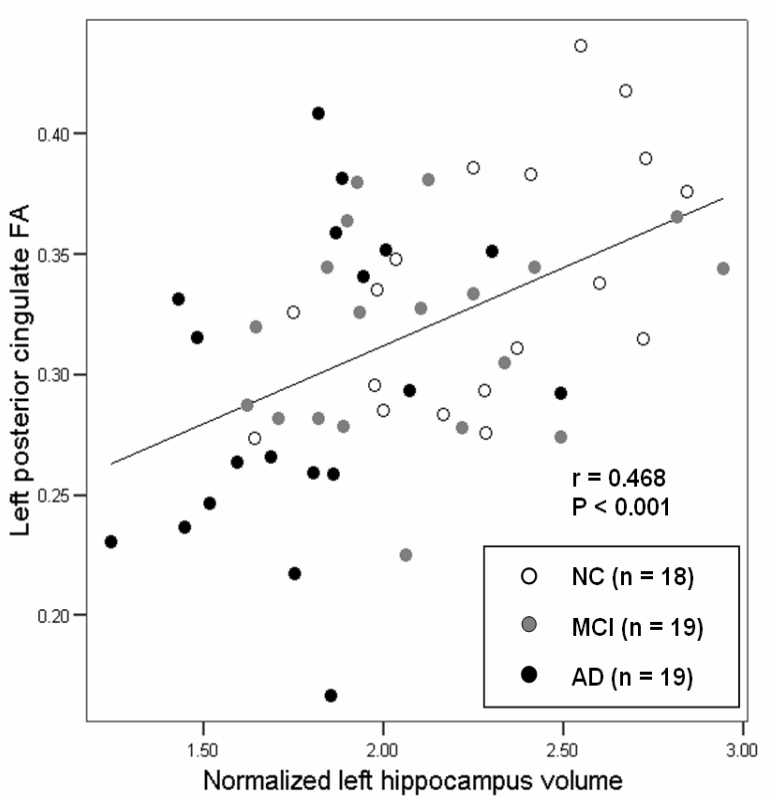
Group comparison by ANCOVA controlling age as a covari

Post-hoc comparison: *CN vs AD, †MCI vs AD..

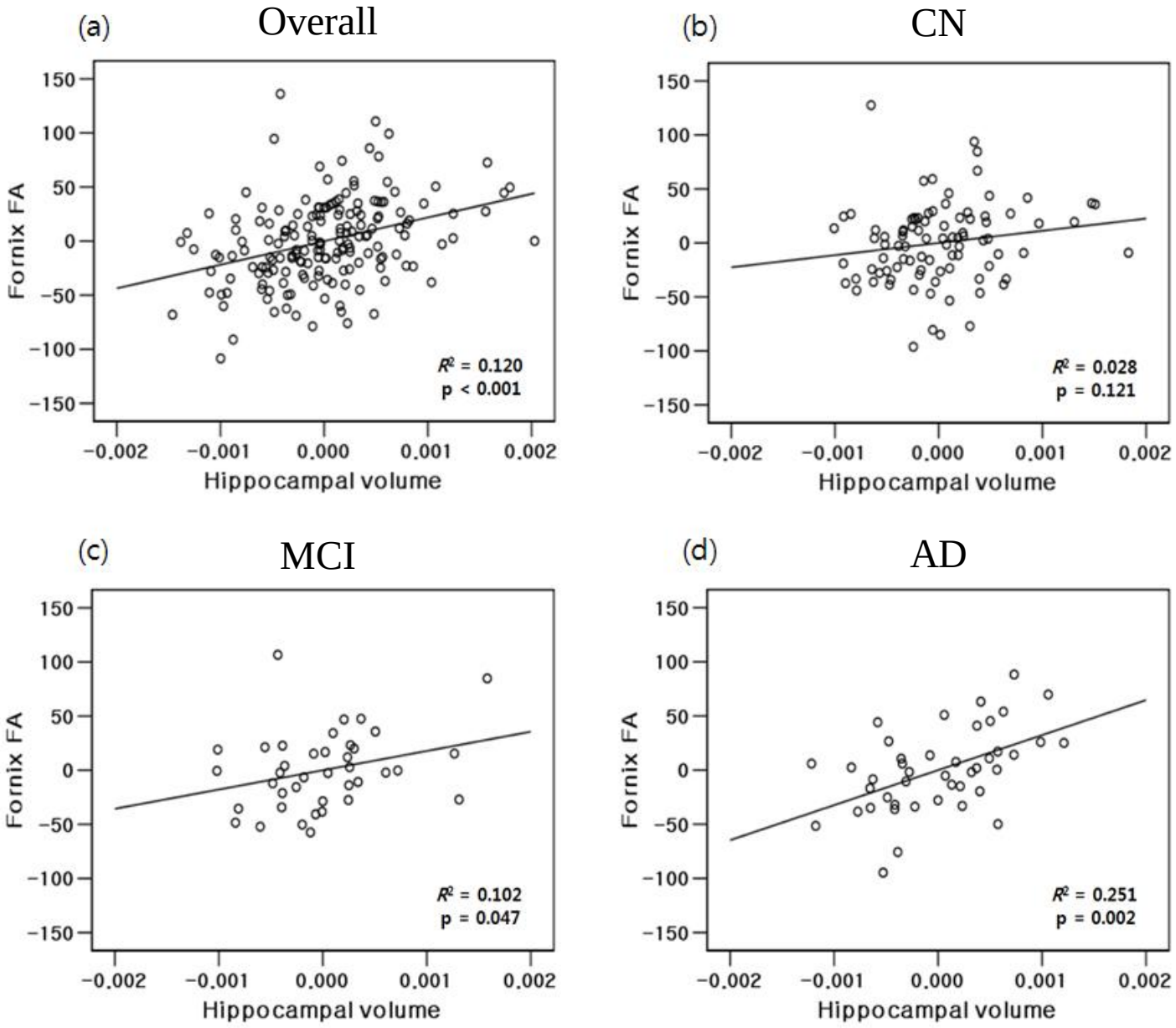
Lee et al. (2009) Neurology

Correlation of MTL volume with the integrity (FA) of PC cingulum





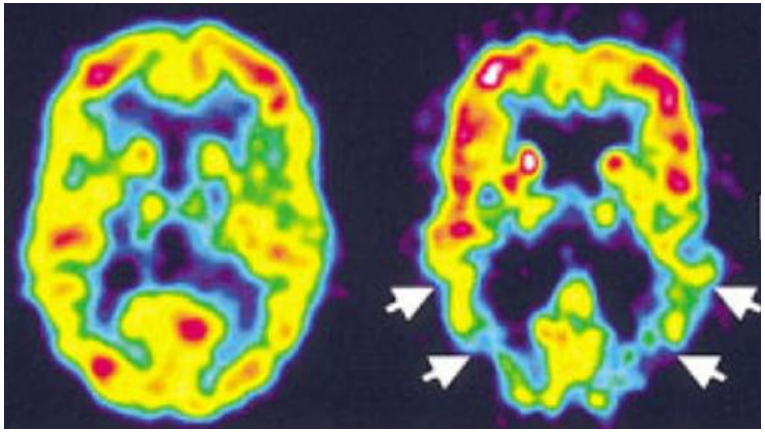
Choo et al. (2010) Neurobiol Aging

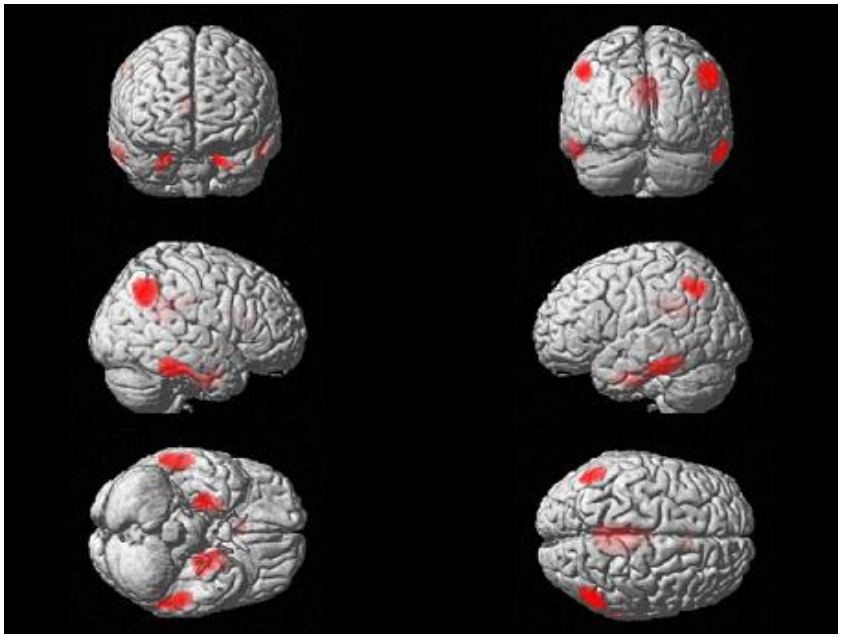


Lee et al. Brain, submitted

FDG-PET: rCMRglu decline in AD

- Parietal and temporal cortex affected
- Relative sparing of primary sensorimotor and primary visual cortex
- **Reflect synaptic dysfunction**

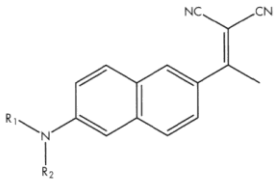




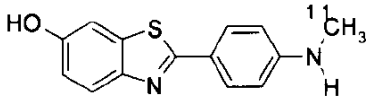
Lee et al., (2008) Dement Geriatr Cogn Disord

PET amyloid Imaging

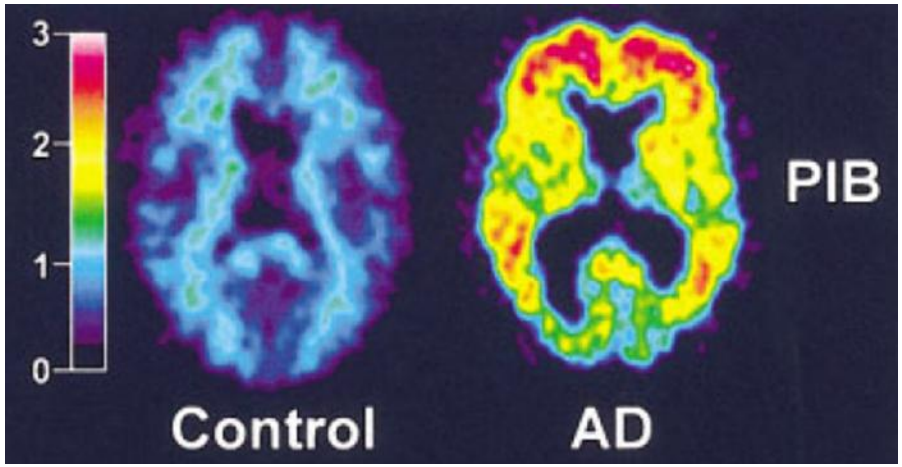
- [^{18}F] FDDNP : imaging of NFT & AP
- [^{11}C] PIB (Pittsburgh Compound-B) : imaging of AP

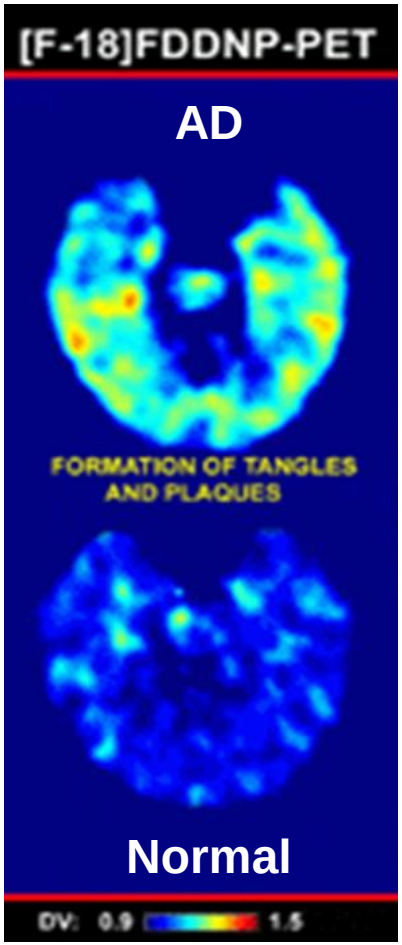


1: R_1=FCH_2CH_2; R_2=CH_3
2: R_1=R_2=CH_3
3: R_1=$HOCH_2CH_2$; R_2=CH_3
4: R_1=$CH_3C_6H_4SO_2OCH_2CH_2$; R_2=CH_3



[*N*-methyl-^{11}C]PIB



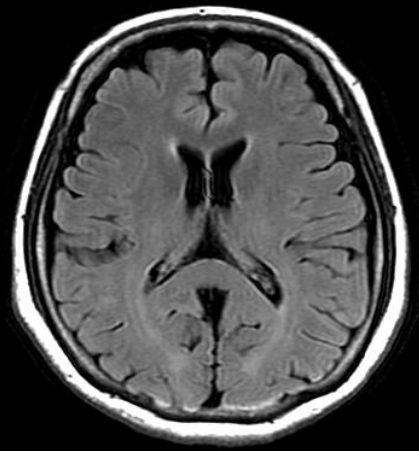


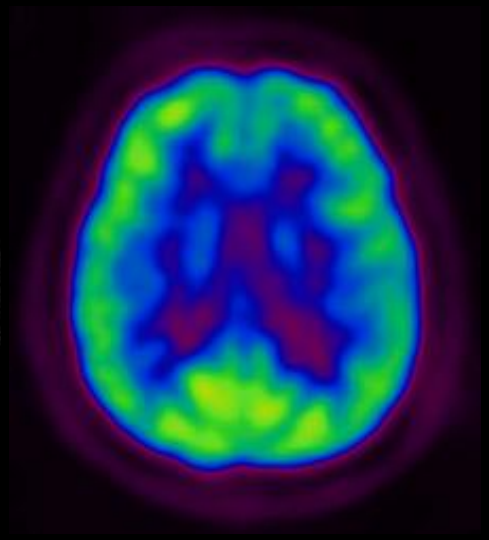
Shoghi-Jadid et al (2002) AJGP; Klunk et al.(2004) Ann Neurol

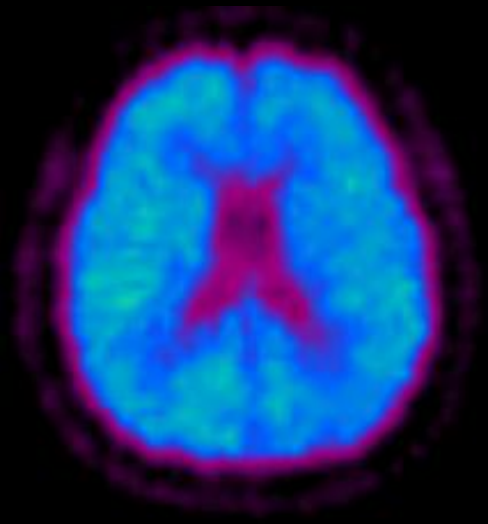
Evolution of amyloid deposits in AD

Braak & Braak. Acta Neuropathol 1991

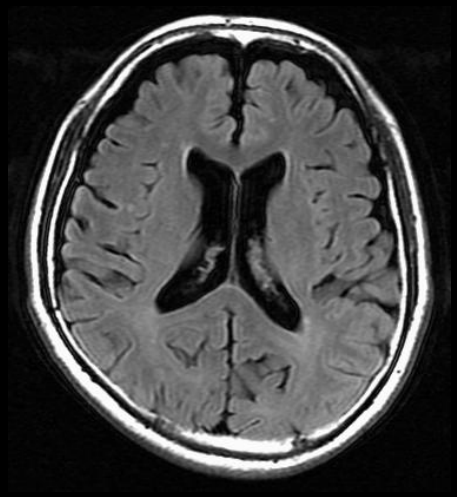
Cognitively normal

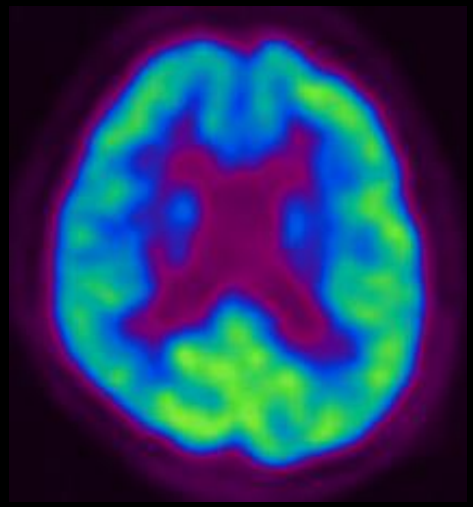


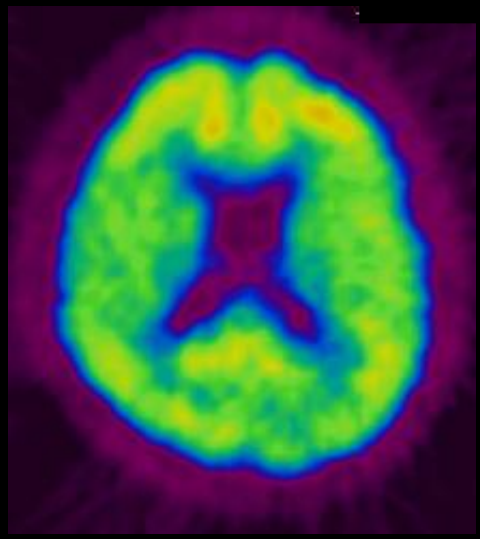




Cognitively normal







MRI (FLAIR)

FDG-PET

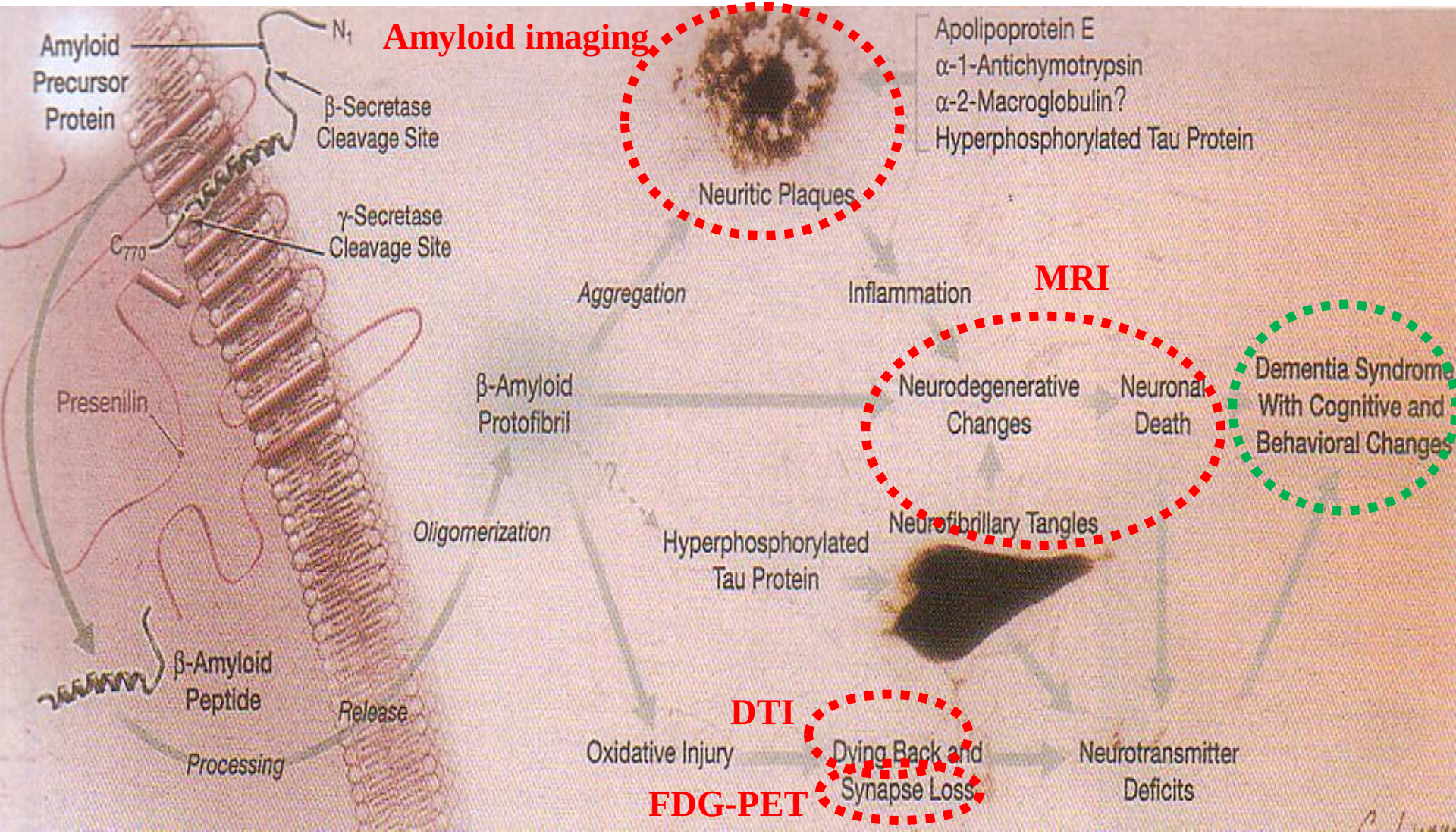
PIB-PET

New ligands for PET amyloid Imaging

- **^{18}F florbetapir** (AV-45)
- **^{18}F florbetaben** (BAY94-9172 or AV-1/Zken)
- **^{18}F flutemetamol** (AF110690)
- **^{18}F SNUBH-NM-333**

Pathogenesis & Neuroimaging Biomarkers of AD : Summary

AD Imaging



Application of Neuroimaging Biomarkers in Alzheimer's Disease

- **For better diagnosis of AD**
  - To increase the diagnostic accuracy of AD in clinical setting
  - To predict future development of AD at preclinical stage
- **For progression monitoring of AD**
  - To measure disease progression in AD in clinical setting
  - To use as a surrogate marker in clinical trials for AD
- **For better understanding of clinico-pathological relationships in AD**

For better Dx of AD:

Incremental diagnostic gain by MTA assessment

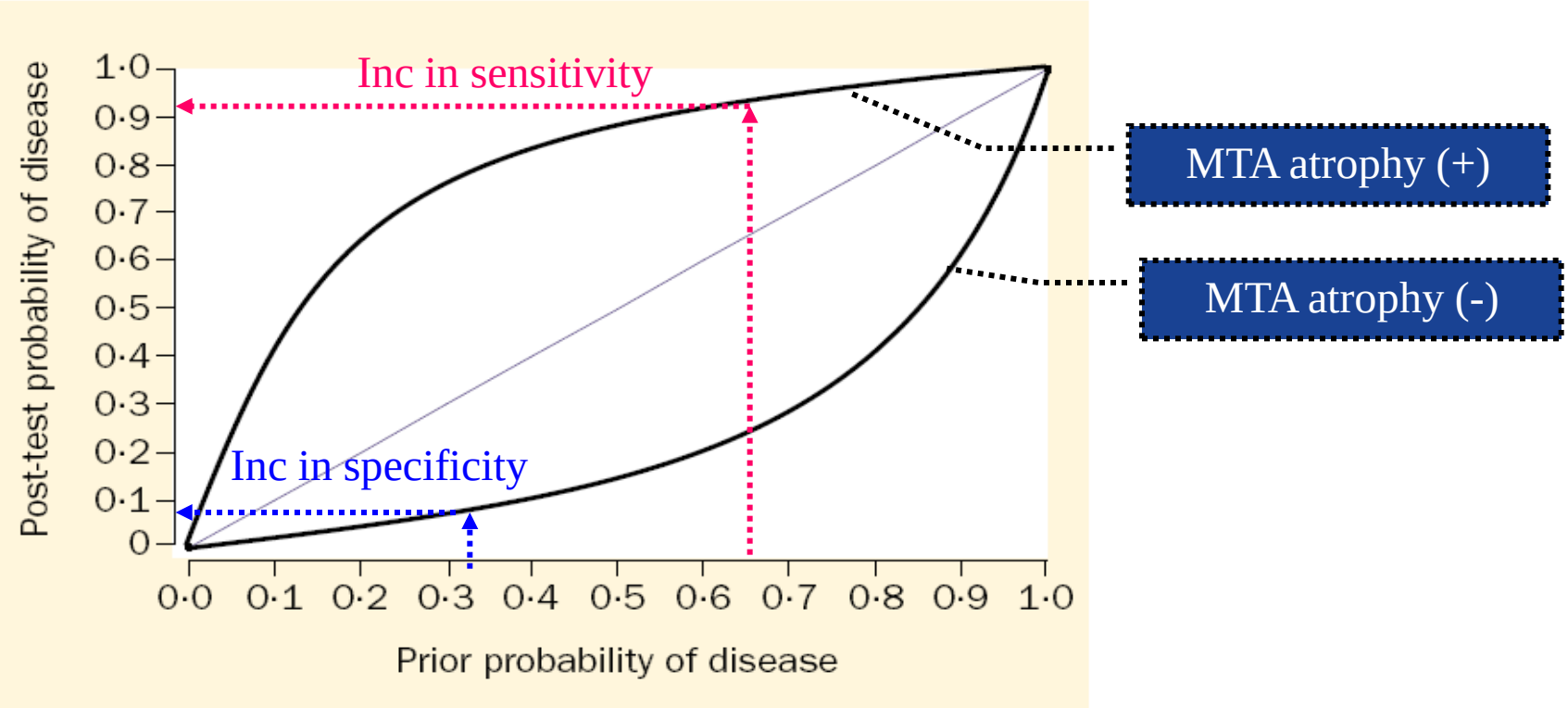


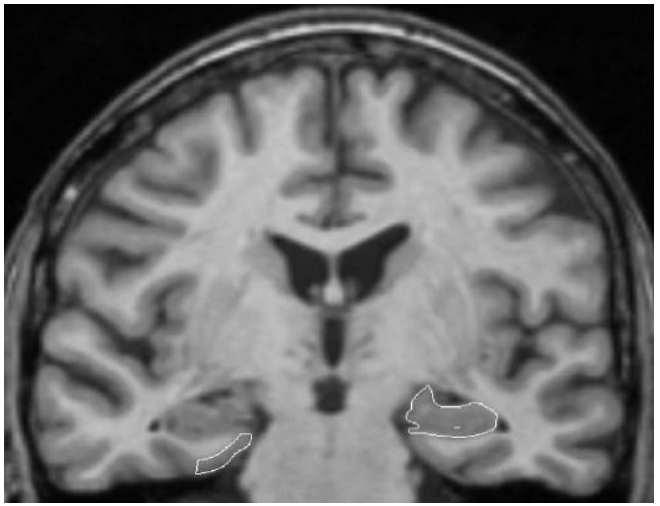
Figure 3. Post-test probability of disease with a test of sensitivity 85% and specificity 88% for any given pretest probability (prevalence of disease). The upper curve shows the incremental diagnostic gain from a positive result of a test (ie, presence of hippocampal atrophy on MRI) and the lower curve shows that from a negative result (ie, Absence of hippocampal atrophy on MRI).

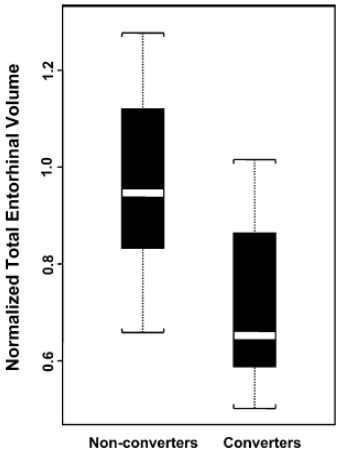
Scheltens (2002) Lancet Neurlogy

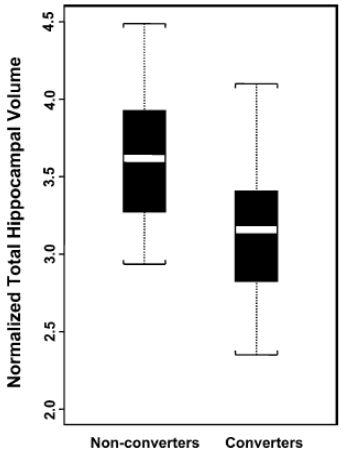
For better Dx of future AD dementia

Prediction of AD with MRI in MCI

- MRI
  - Hippocampal and entorhinal cortex atrophy
    - Consistently reported to have predictive value
  - Accurate prediction rate reported
    - **74 ~ 93% (80%)**







deToledo-Morrell et al. (2004) Neurobiol Aging

For better Dx of AD:

Dx accuracy of FDG-PET in AD

- Compared with neuropathological confirmation of presence or absence of AD

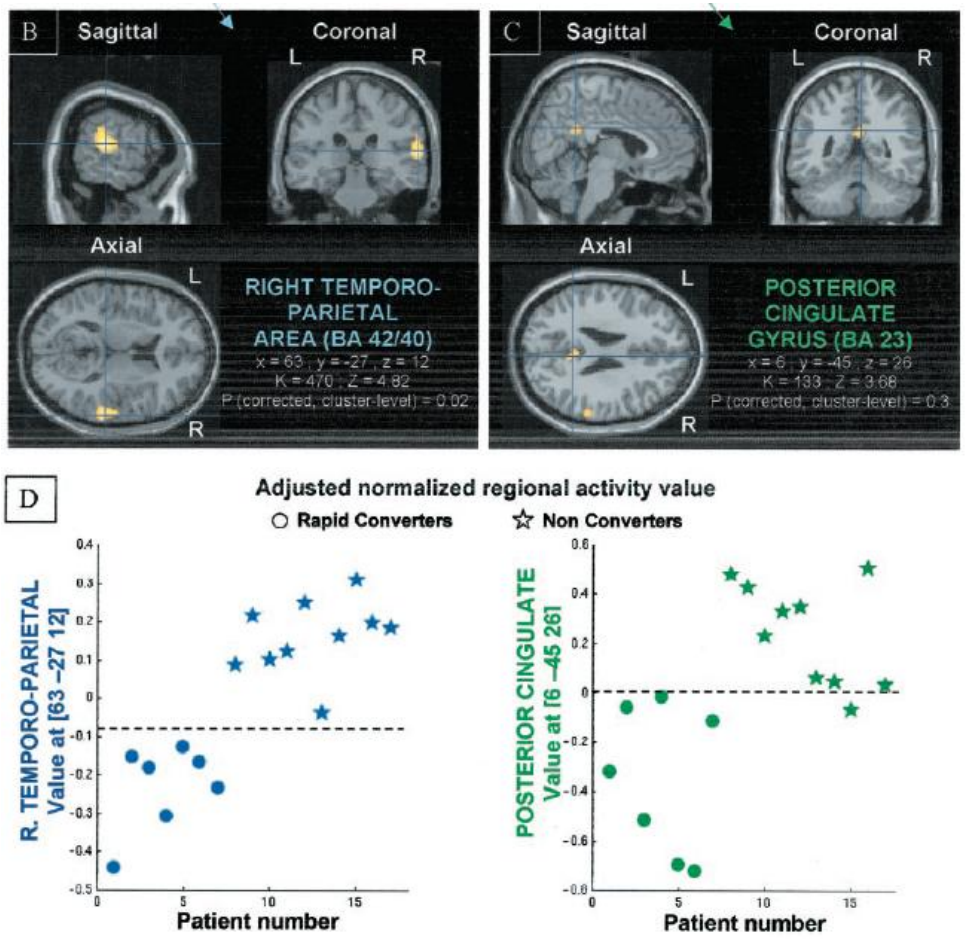
Basis of AD diagnosis	Sensitivity	Specificity
Clinical evaluation, probable AD	66% ± 17%	77% ± 23%
Clinical evaluation, probable + possible AD	90.5% ± 5.5%	55.5% ± 5.5%
^{18}F-FDG PET, AD pattern	91.5% ± 3.5%	70% ± 3%

Silverman (2004) J Nucl Med

For better Dx of future AD dementia

Prediction of AD with FDG-PET

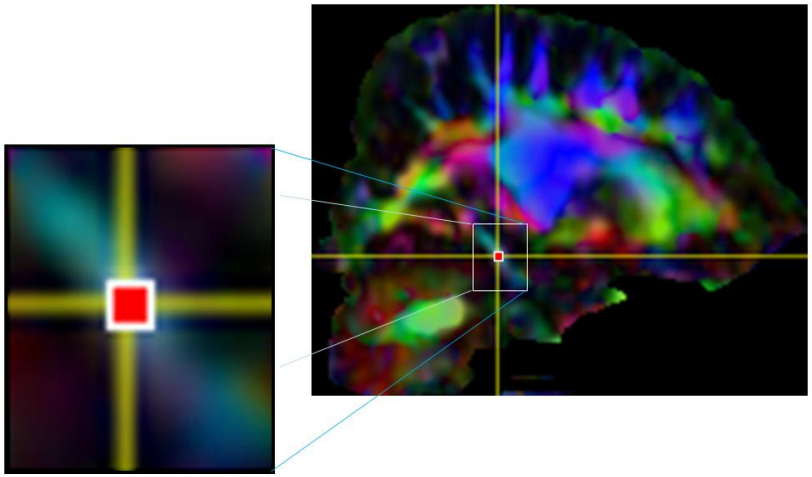
- PET
  - Posterior cingulate
  - Temporoparietal cortex
  - Hippocampal formation
  - Accurate prediction rate
    - 65 ~ 94% (80%)

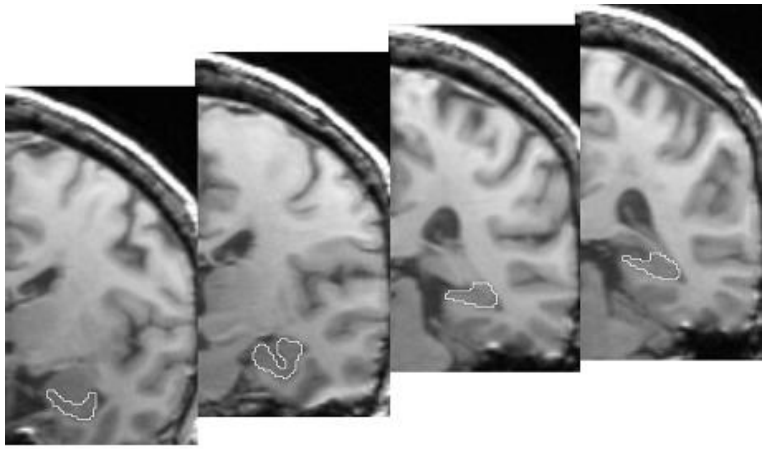


Chetelat et al. (2003) Neurology

Discrimination of normal aging, MCI and AD with multimodal imaging measures on the medial temporal lobe

Jin Hyeong Jhoo[a], Dong Young Lee[b,c,*], Il Han Choo[b], Eun Hyun Seo[c], Jungsu S. Oh[b], Jae Sung Lee[d], Dong Soo Lee[d], Shin Gyeom Kim[e], Jong Chul Youn[f], Ki Woong Kim[g], Jong Inn Woo[b,c,h]





Jhoo et al. (2010) Psychiatry Res Neuroimaging

Results obtained from logistic regression analyses designed to select appropriate models for discrimination between NC and MCI.

Models	Variable	−2LL	χ^2	*df*	*P*-value	Diagnostic Accuracy (%)	Significance test* for −2LL difference
One candidate model							
Model V:	HC-Vol	42.68	4.45	2	0.108	70.6	
Model F:	PHC-FA	38.23	8.91	2	0.012	73.5	
Model G:	HC-Glu	47.05	0.08	2	0.959	50.0	
Two candidate model							
Model FV:	**PHC-FA+ HC-Vol**	**30.44**	**16.70**	**3**	**0.001**	**79.4**	**Model FV vs. F: *P*= 0.005**
Model FG:	PHC-FA+ HC-Glu	38.21	8.92	3	0.030	70.6	Model FG vs. F: *P*= 1.000
Three candidate model							
Model FVG:	PHC-FA+ HC-Vol+ HC-Glu	30.20	16.93	4	0.002	79.4	Model FVG vs. FV: *P*= 0.990

Jhoo et al. (2010) Psychiatry Res Neuroimaging

Proposed recommendations to update diagnostic criteria for AD

- Based on U.S. NIA and AA-organized project
- Preliminary reports presented in July 2010 AAICAD

Three Parts (workgroups)

- Criteria for **AD dementia** (McKhann G. et al.)
- Criteria for **MCI due to AD** (Albert M. et al.)
- Criteria for **Preclinical AD** (Sperling R. et al.)

Criteria for AD dementia

I. Criteria for all-cause Dementia
   - Interfere with work or social activities
   - A decline from prior levels of functioning
   - Not explained by delirium nor MDD
   - Cognitive impairment in at least two domains, detected through Hx from pt, reliable informant and objective cognitive assessment

II. Criteria for the Dx of AD Dementia
   - Insidious onset
   - Clear-cut history of worsening of cognition
   - Cognitive deficits in one of the two categories

Clinical AD Dementia – Degrees of Certainty

A. Probable AD dementia

B. Possible AD dementia

Criteria for AD dementia

AD Imaging

A. Probable AD dementia (II + one of the three)

1. Documented progressive cognitive decline on subsequent evaluation **OR**
2. **Biomarker positive (one of more) OR**
   - Low CSF Aβ42, elevated CSF tau or p-tau
   - Positive amyloid PET imaging
   - Decreased FDG-PET in T-P
   - Disproportionate atrophy on sMRI: MTA, other temporal, parietal
3. Mutation carrier (PSEN1, PSEN2, APP)

B. Possible AD dementia (II + one of the three)

- Atypical course: no A1 **OR**
- **Biomarkers obtained and negative OR**
- Mixed presentation
  - Concomitant CVD OR
  - Evidence for some feature of DLB that do not achieve a level of probable DLB Dx.

Criteria for MCI due to AD

AD Imaging

I. Criteria for Clinical and Cognitive Syndrome

- Concern regarding a change in cognition
- Impairment in one or more cognitive domain
- Preservation of independence in functional abilities
- Not demented

II. MCI due to AD with varying levels of certainty

1. MCI due to a neurodegenerative etiology
   - Negative or ambiguous BM evidence for AD neuropathology
2. MCI of Alzheimer type
   - A positive topographic BM & untested molecular BM
   - A positive topographical BM & negative or ambiguous molecular BM
3. **Prodromal Alzheimer's Dementia**
   - A positive molecular BM and normal or equivocal topographical BM
   - **A positive molecular BM and a positive topographic BM (Highest)**

Criteria for Preclinical AD

Stage 1: Asymptomatic cerebral amyloidosis

(on amyloid imaging or CSF Aβ assay)

Stage 2: Amyloid positivity

+ evidence of neurodegeneration

(on FDG-PET and/or MRI)

Stage 3: Amyloid positivity

+ evidence of neurodegeneration

+ subtle cognitive decline

(on cognitive tests, but not meeting MCI criteria)

For progression monitoring of AD:
Brain Boundary Shift Integral (BSI) method

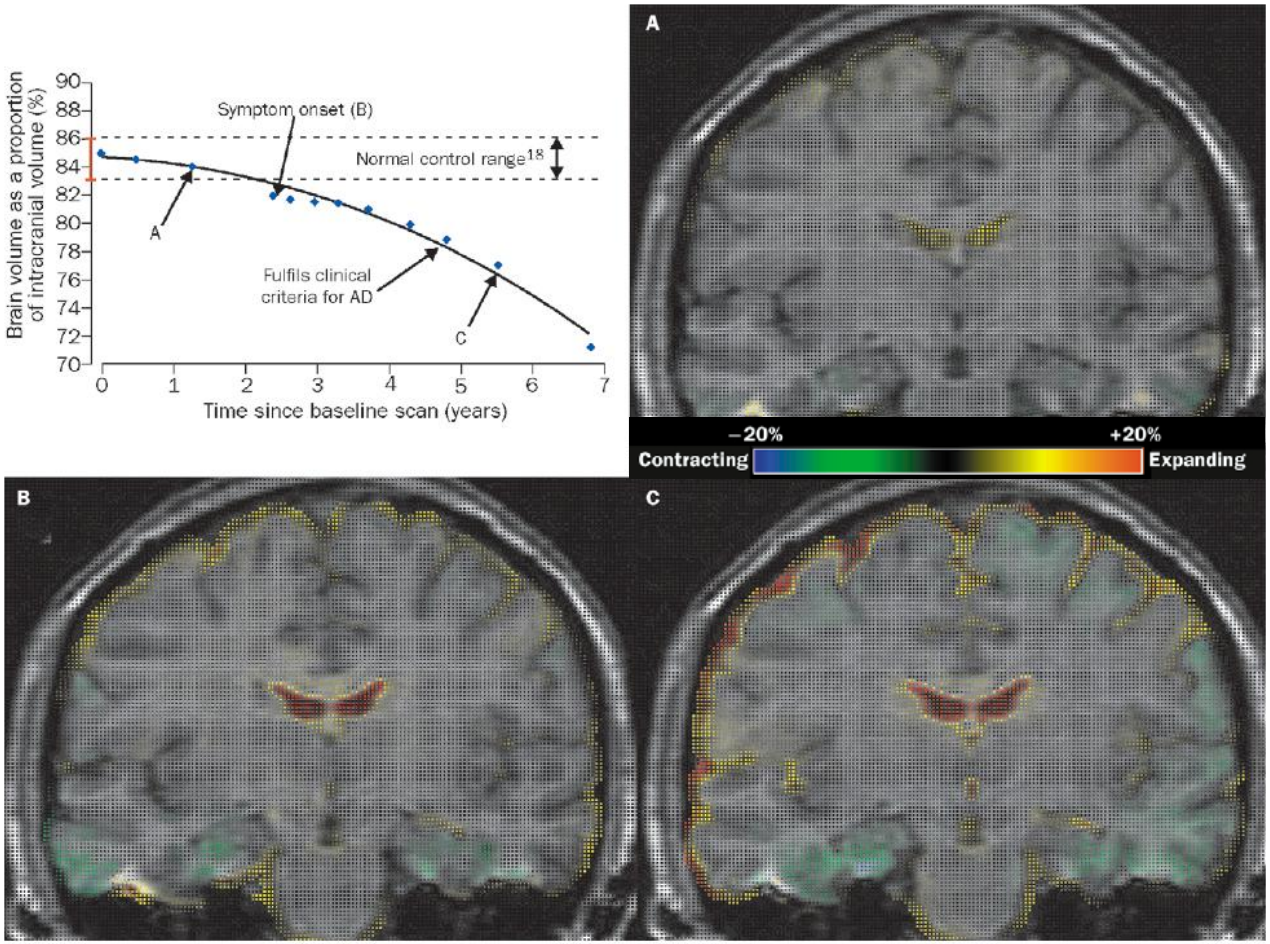


Figure 4: **Change in brain volume as percentage of intracranial volume over time in a woman with familial Alzheimer's disease who was 36 years old at baseline**

Fox et al. (2001) Lancet

For progression monitoring of AD:

Estimated number of AD subjects per arm between cognitive tests and MRI volume measures

AD Imaging

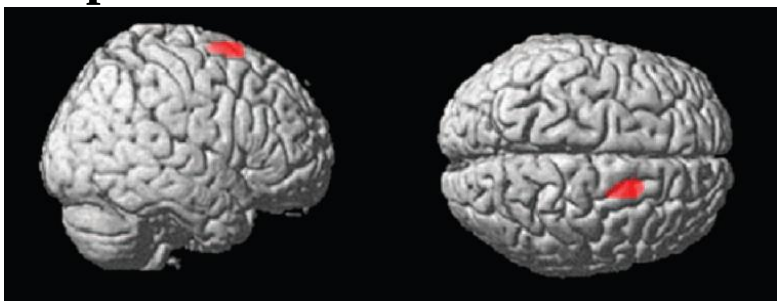
- To detect a 50% reduction in the rate of decline over one year

Measures	ADAS-cog	MMSE	Hippocampus volume	Temporal horn volume
Subjects number per arm	320	241	21	54

Jack et al. (2003) Neurology

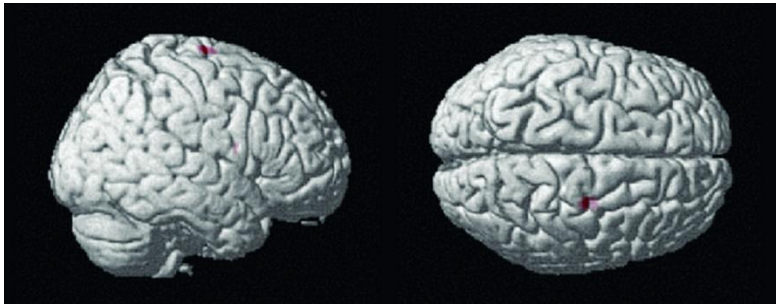
Understanding brain-behavior relationships with neuroimaging:

Depression in AD



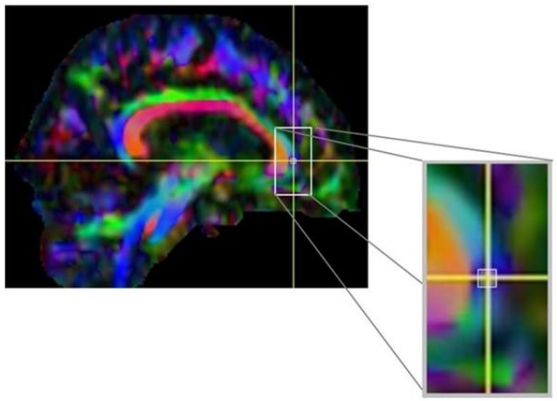
Lee et al. (2006) Am J Geriatr Psychiatry

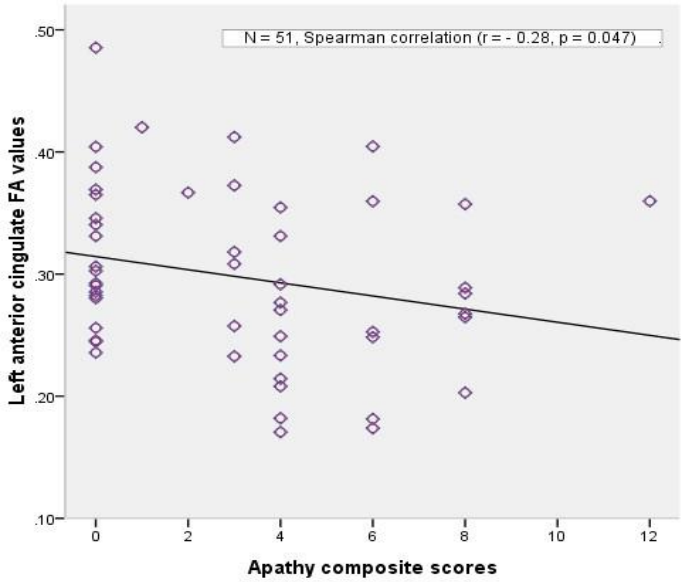
Depression in MCI



Lee et al. (2010) Psychiatr Invest

Apathy in AD



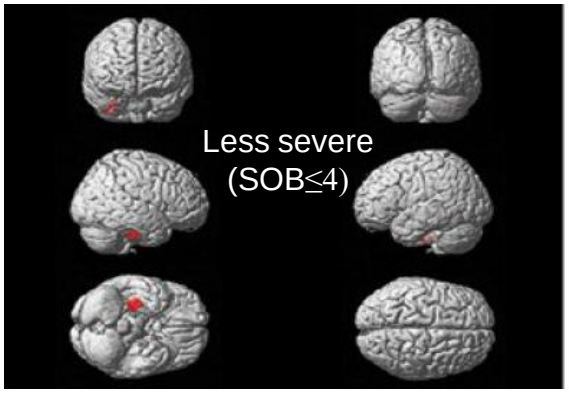


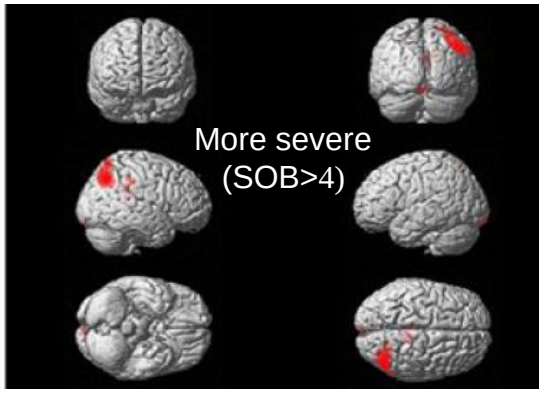
Kim et al. Am J Geriatr Psychiatry (accepted)

Understanding brain-behavior relationships with neuroimaging:

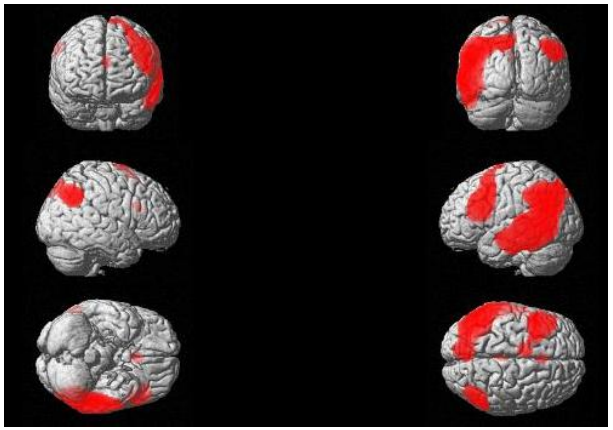
Clock drawing performance in AD

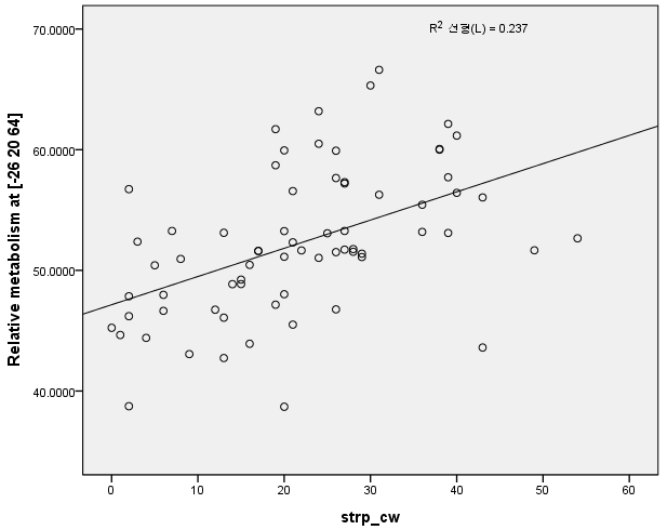
Lee et al. (2008) Dementia Geriatr Cog Disd





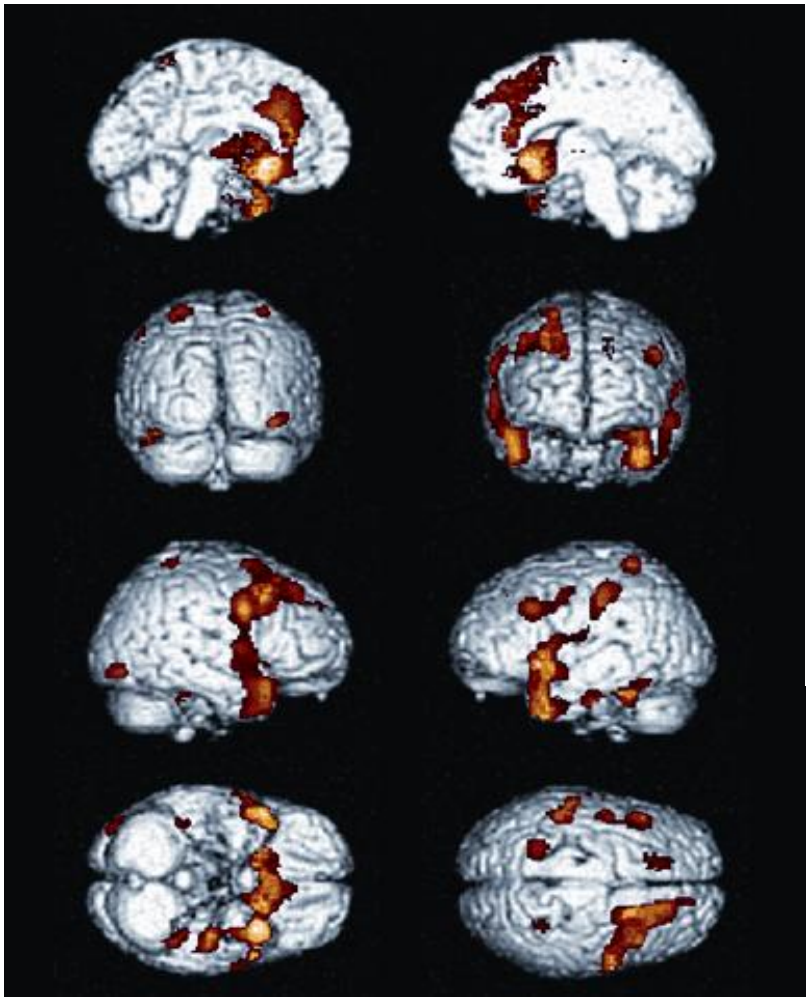
Stroop performance in AD

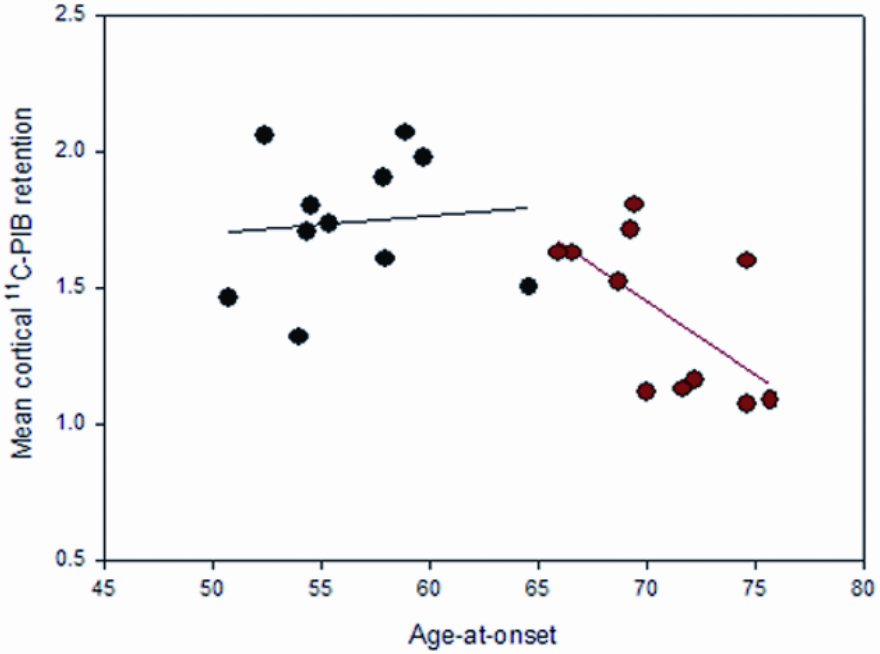




SNUH Dementia Clinic (prepared)

Relationship of amyloid-beta burden with age-at-onset in Alzheimer's disease





Choo et al. Am J Geriatr Psychiatry (accepted)

Conclusion

- Neuroimaging biomarkers well reflect in vivo pathological changes that characterize AD process.

- Neuroimaging biomarkers could be well applied to improve AD diagnosis, progression monitoring, and understanding clinico-pathological relationship.