Neuroimaging – Alzheimer's disease and allied dementing conditions

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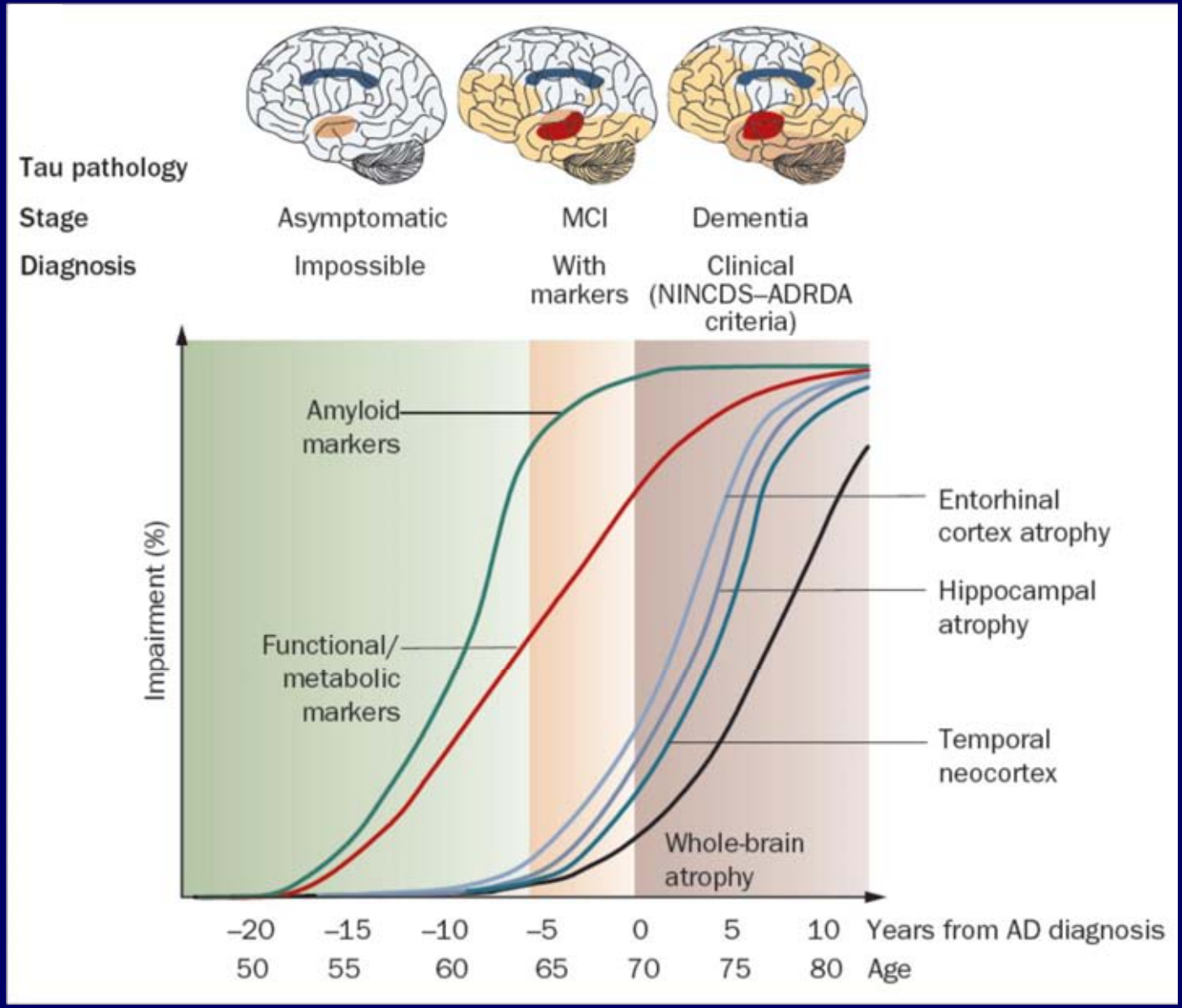
NEUROIMAGING IN DEMENTIA

Outline of the presentation

- **Alzheimer's disease (AD)**
- **Frontotemporal lobar degeneration (FTLD)**

NEUROIMAGING IN DEMENTIA

Background / AD theoretical model



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AD / Revised diagnostic criteria

AD dementia criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (CSF tau, FDG-PET, structural MRI)
Probable AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With three levels of evidence of AD pathophysiological process	Intermediate	Unavailable or indeterminate	Positive
	Intermediate	Positive	Unavailable or indeterminate
	High	Positive	Positive
Possible AD dementia (atypical clinical presentation)			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
Dementia-unlikely due to AD	Lowest	Negative	Negative

McKhann et al., Alzheimer's & Dementia 2011

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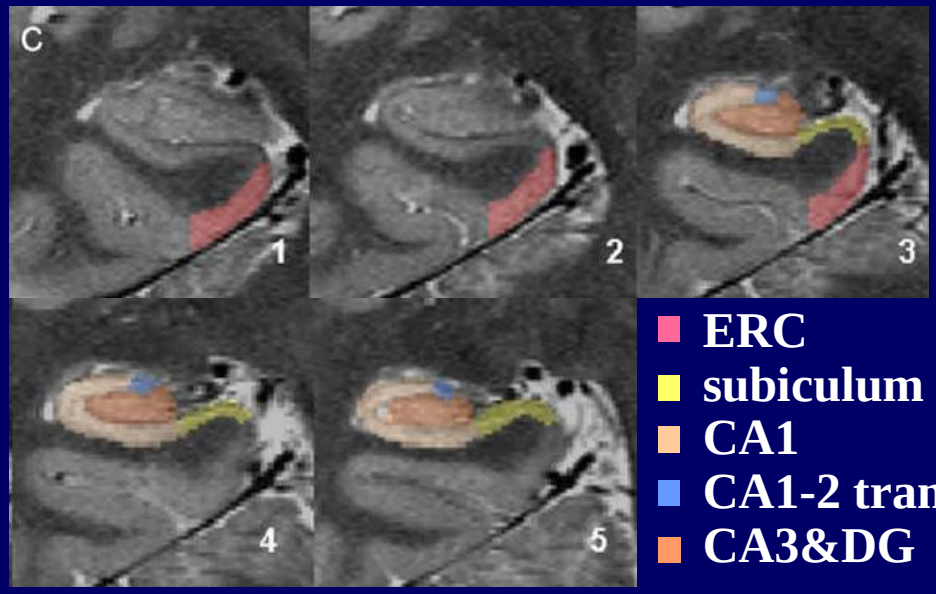
AD / Biomarkers

Hippocampus (4 T scanner)



- ERC
- subiculum
- CA1
- CA1-2 transition
- CA3&DG

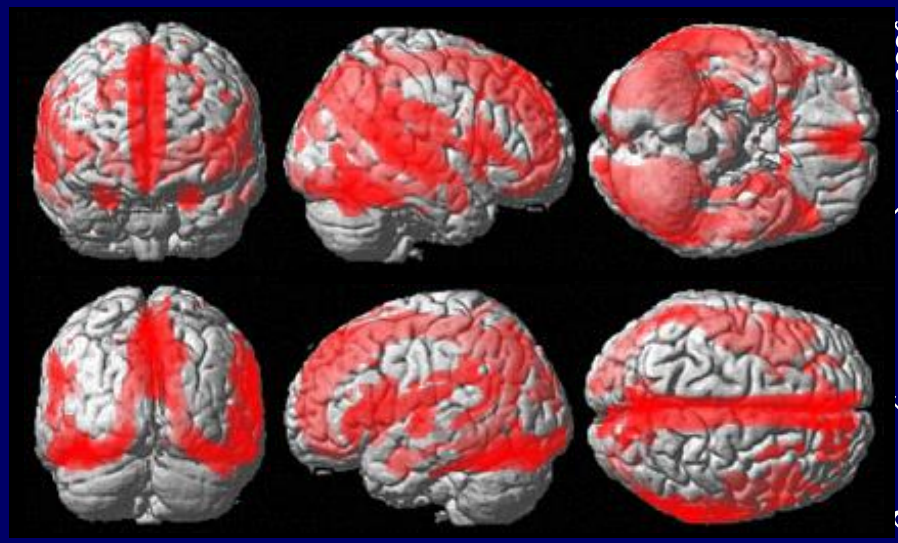
Apostolova et al., Hippocampus 2006

TABLE II. Mean and standard deviation of subfield and total hippocampal volumes in mm^3

	Control ($n = 53$)	MCI ($n = 20$)	AD ($n = 18$)
ERC	190.7 ± 54.4	167.4 ± 44.3	144.4 ± 48.3*
Subiculum	190.9 ± 37.8	184.6 ± 31.5	154.7 ± 45.1*
CA1	325.7 ± 48.3	296.9 ± 43.5	271.1 ± 58.0*
CA1-2 transition	19.33 ± 5.4	14.8 ± 2.5*	14.0 ± 3.4*
CA3 & DG	225.6 ± 40.7	230.7 ± 32.1	225.7 ± 49.7
Total hippocampus	5487.6 ± 770.7	5123.2 ± 752.0	4615.9 ± 1182.5*

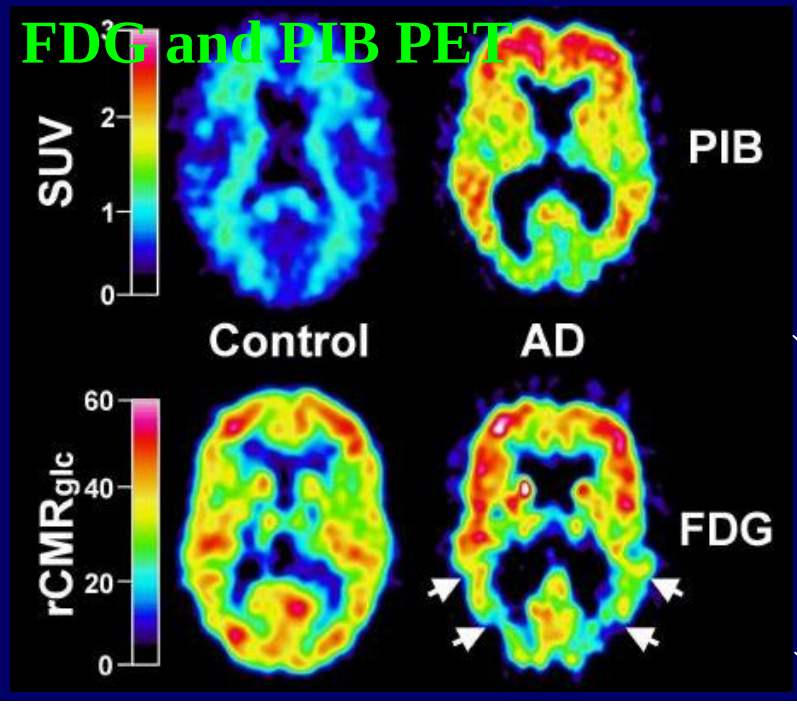
AD

Control



Mosconi, Brain and Cognition, 2009

FDG and PIB PET



Klunk et al., Ann Neurol 2004

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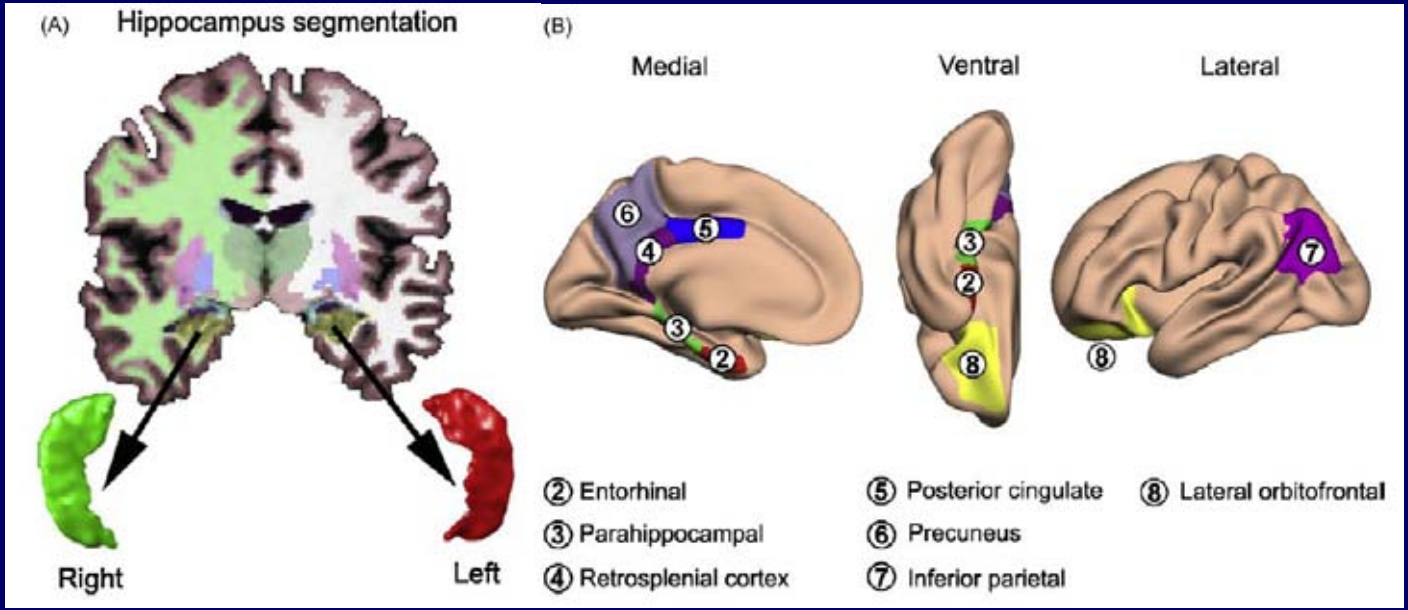
AD / Neural correlates of memory deficits



Stepwise regression analyses for the total sample with learning score (hits minus intrusions) as the dependent variable

	β	p	R^2	F	Model p
Total sample					
Model I					
MR Hippocampus	.45	.000	.20	40.091	.000
Model II					
MR Hippocampus	.45	.000			
PET Hippocampus	.26	.000	.27	29.312	.000
Model III					
MR Hippocampus	.40	.000			
PET Hippocampus	.26	.000			
MR Precuneus cortex	.17	.017	.30	22.073	.000
Model IV					
MR Hippocampus	.35	.000			
PET Hippocampus	.15	.046			
MR Precuneus cortex	.22	.002			
PET Inferior parietal cortex	.23	.005	.32	19.383	.000

Stepwise regression analysis for the total sample with recognition (hits minus errors) as the dependent variable

	β	p	R^2	F	Model p
Total sample					
Model I					
MR Hippocampus	.47	.000	.22	44.850	.000
Model II					
MR Hippocampus	.47	.000			
PET Hippocampus	.28	.000	.30	33.890	.000
Model III					
MR Hippocampus	.40	.000			
PET Hippocampus	.29	.000			
MR Parahippocampal cortex	.17	.018	.33	25.160	.000
Model IV					
MR Hippocampus	.34	.000			
PET Hippocampus	.25	.000			
MR Parahippocampal cortex	.17	.018			
APOE	.15	.047	.34	20.230	.000

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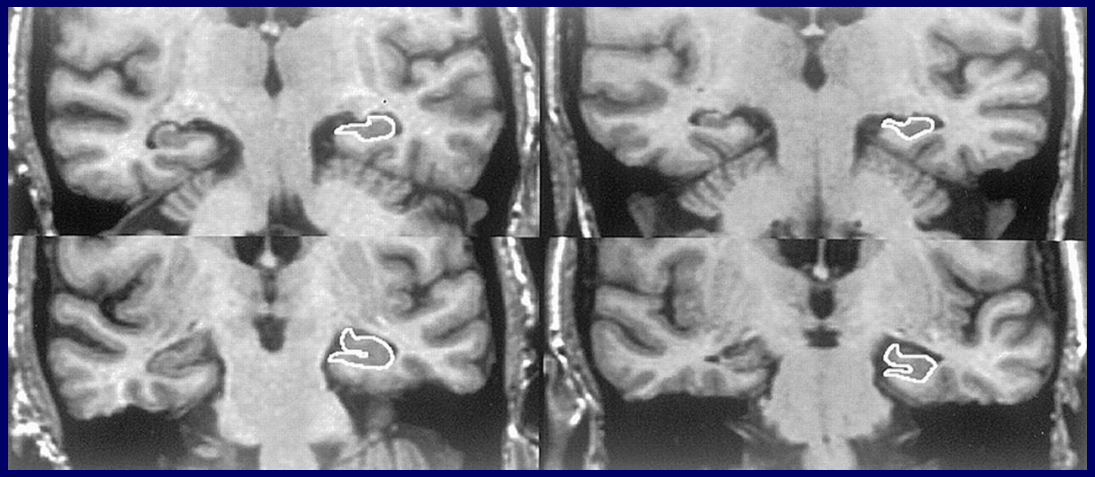
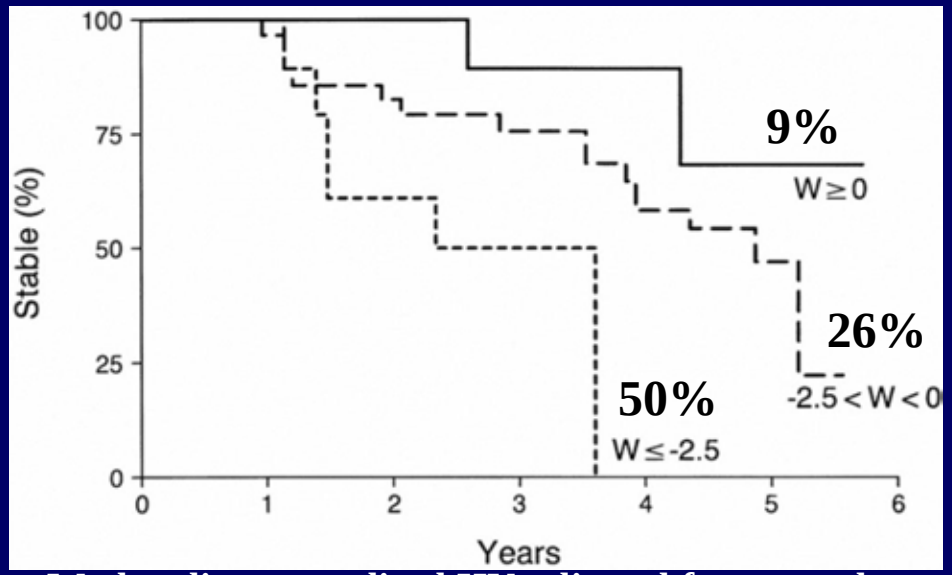
MCI and normals → AD / Hippocampal atrophy

80 MCI, FU 32 months, 27 converteres

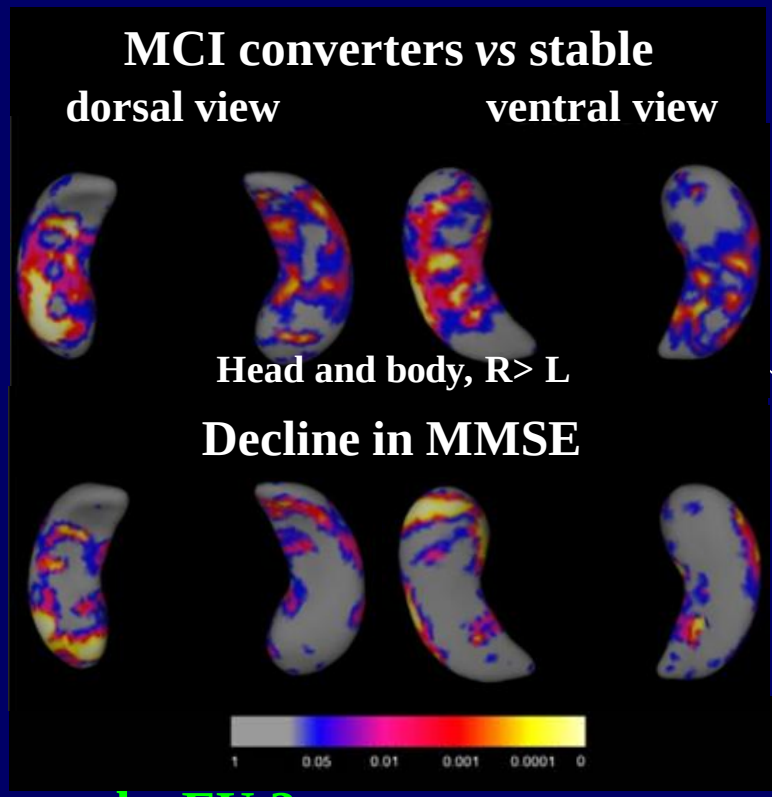




Jedynak, Neuroimage 2009

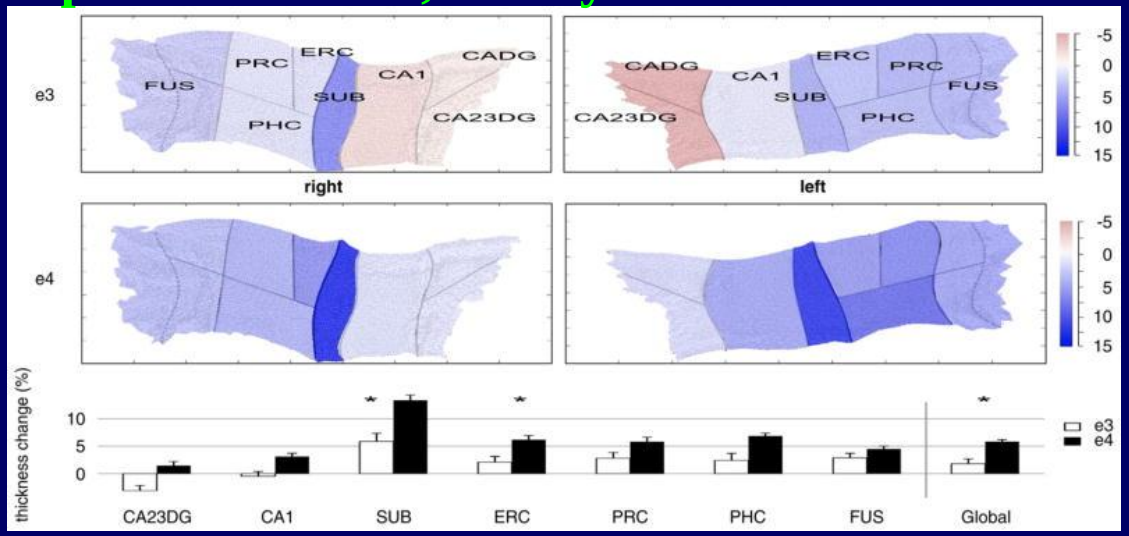
W= baseline normalized HV, adjusted for age and sex

103 MCI, FU 1 year, 22 converters



Costafreda, Neuroimage 2011

ApoE4+ normals, FU 2 yrs

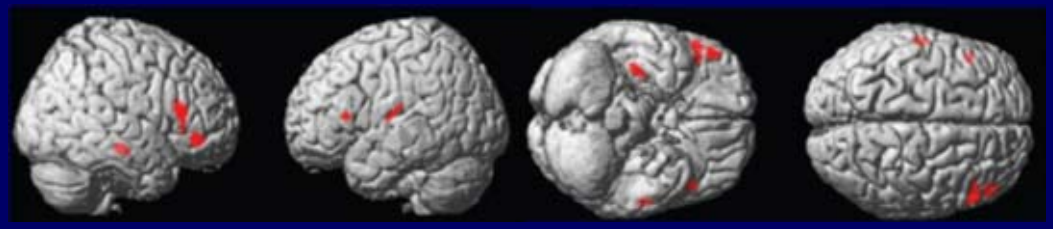


Donix et al., NeuroImage 2010

NEUROIMAGING IN DEMENTIA

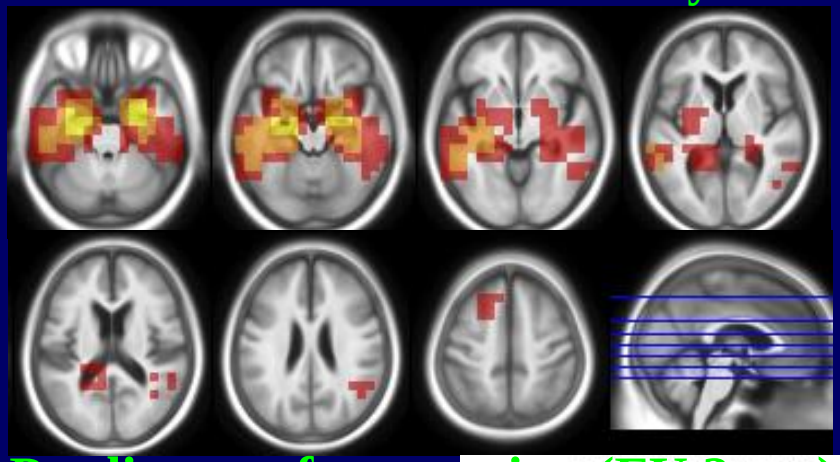
MCI and normals → AD / GM atrophy

Converters *vs.* non-converters (FU 2 yrs)

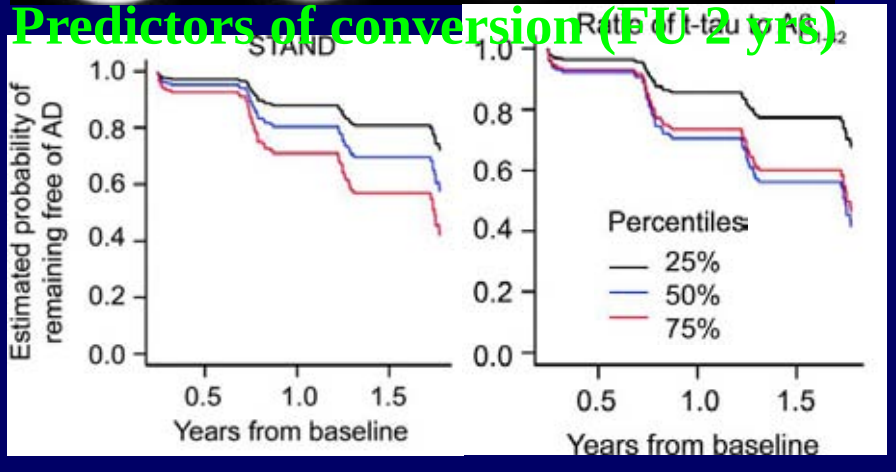


Bozzali, Filippi et al., Neurology 2006

STAND: Structural Abnormality Index

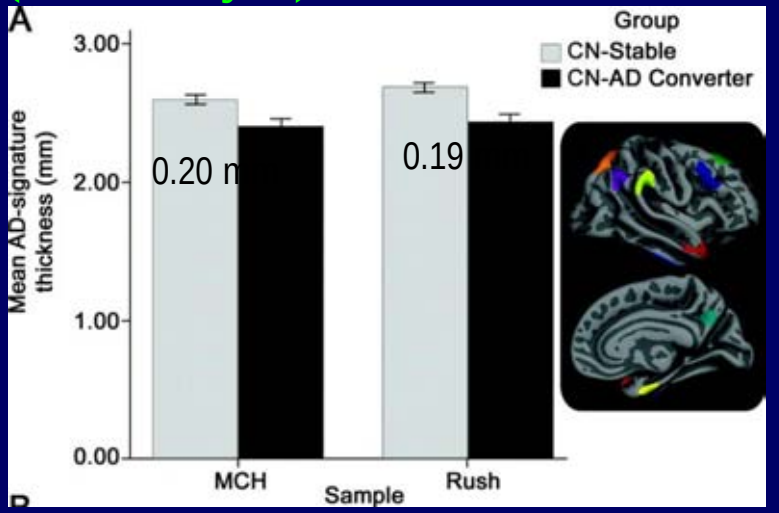


Predictors of conversion (FU 2 yrs)



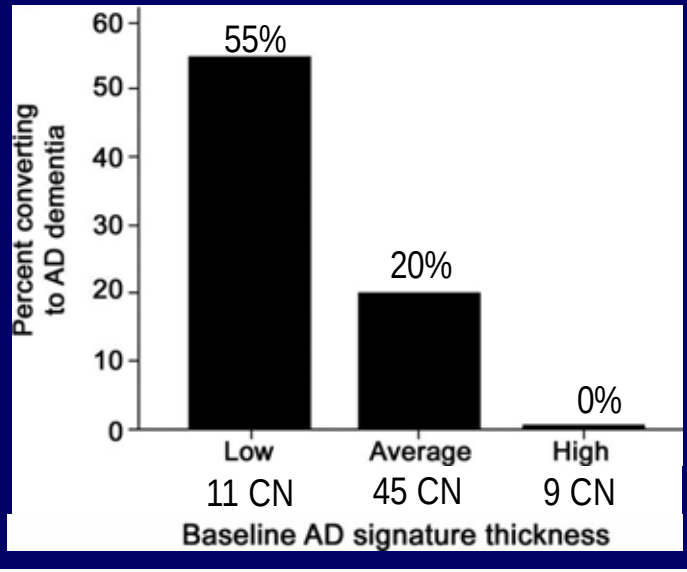
Longitudinal analysis

Thinner cortex in CN-AD converters (FU 7-11 yrs)



Longitudinal analysis

Risk of dementia *vs.* cortical thickness



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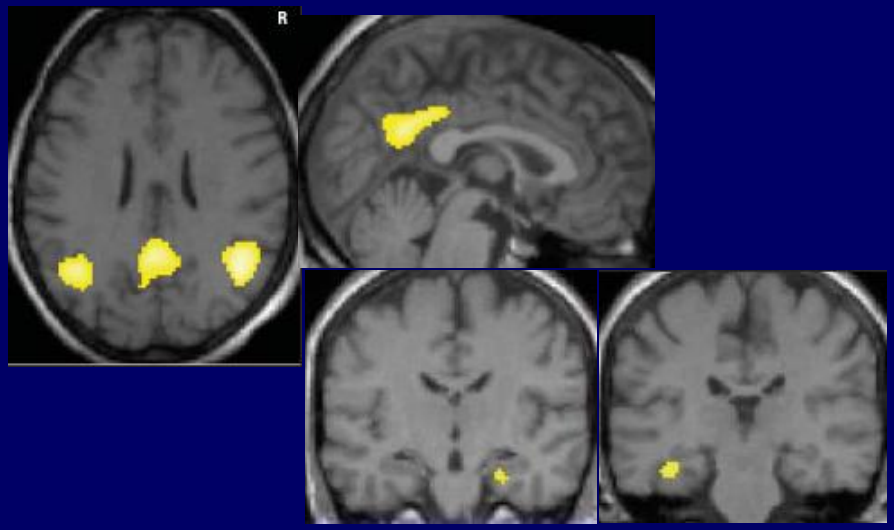
MCI and normals → AD / Metabolic and amyloid imaging changes

FDG PET: MCI converters (FU 12 months)



Mosconi, Brain, 2008

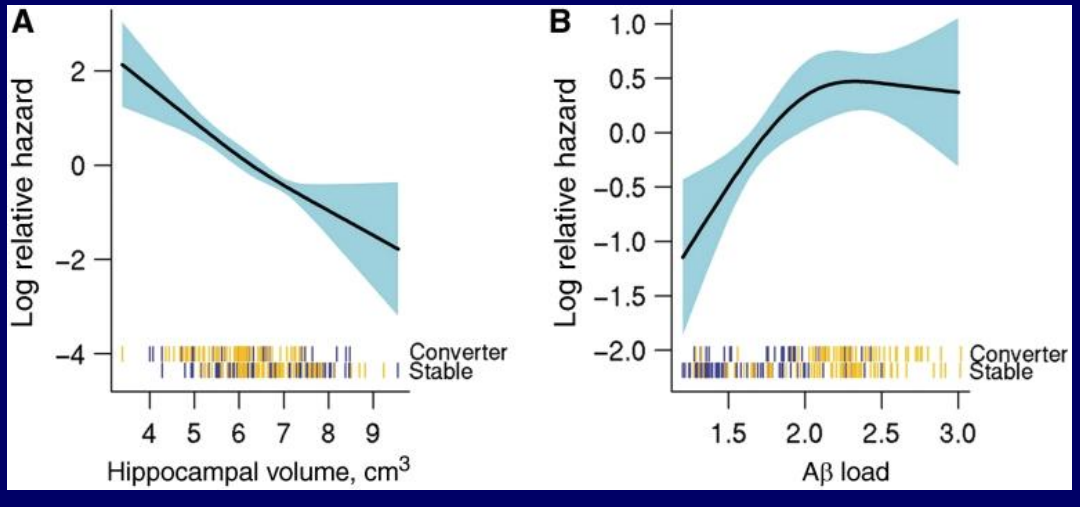
PIB PET: HC converters *vs* nonconverters (FU 20 months)

Characteristic	HC Nonconverter to MCI/DAT	HC Converter to MCI/DAT
Participants, No.	100	6
Age at baseline, yr	72.9±7.4	75.2±8.4
Gender, M/F	48/52	1/5[a]
Years of education	13.2±3.6	13.0±3.3
MMSE at baseline	29.3±0.9	28.2±1.2
CDR at baseline	0.05±0.14	0.33±0.26[a]
CDR-SOB at baseline	0.14±0.42	0.40±0.22
%ApoE ε4	31%	67%
Episodic memory score	−0.11±0.8	−1.28±0.4[a]
Nonmemory score	−0.01±0.7	−0.01±0.4
PiB SUVR	1.4±0.4	2.0±0.6[a]
% high PIB	28%	83%[b]
PiB SUVR increase	0.01±0.06 (0.7%)	0.05±0.04[a] (2.5%)

[a]Significantly different from nonconverters ($p < 0.05$).
[b]Significantly different from nonconverters (Fisher exact test $p < 0.01$).

Villemagne et al., Ann Neurol 2011

HV and PIB PET: Risk profile as a function of increasing biomarker severity in MCI (FU 2 yrs)

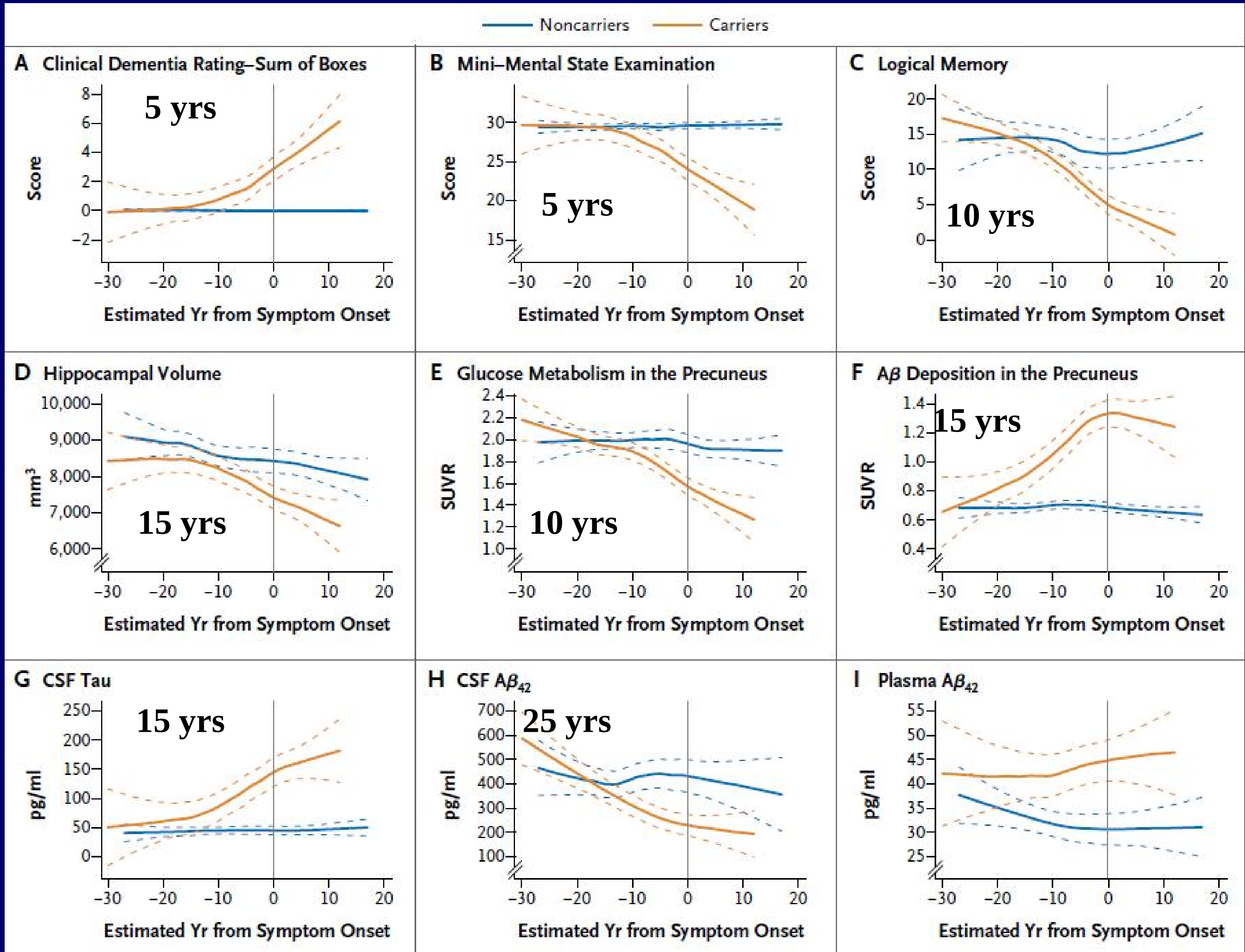


Jack, Brain, 2010

NEUROIMAGING IN DEMENTIA

Dominantly inherited AD

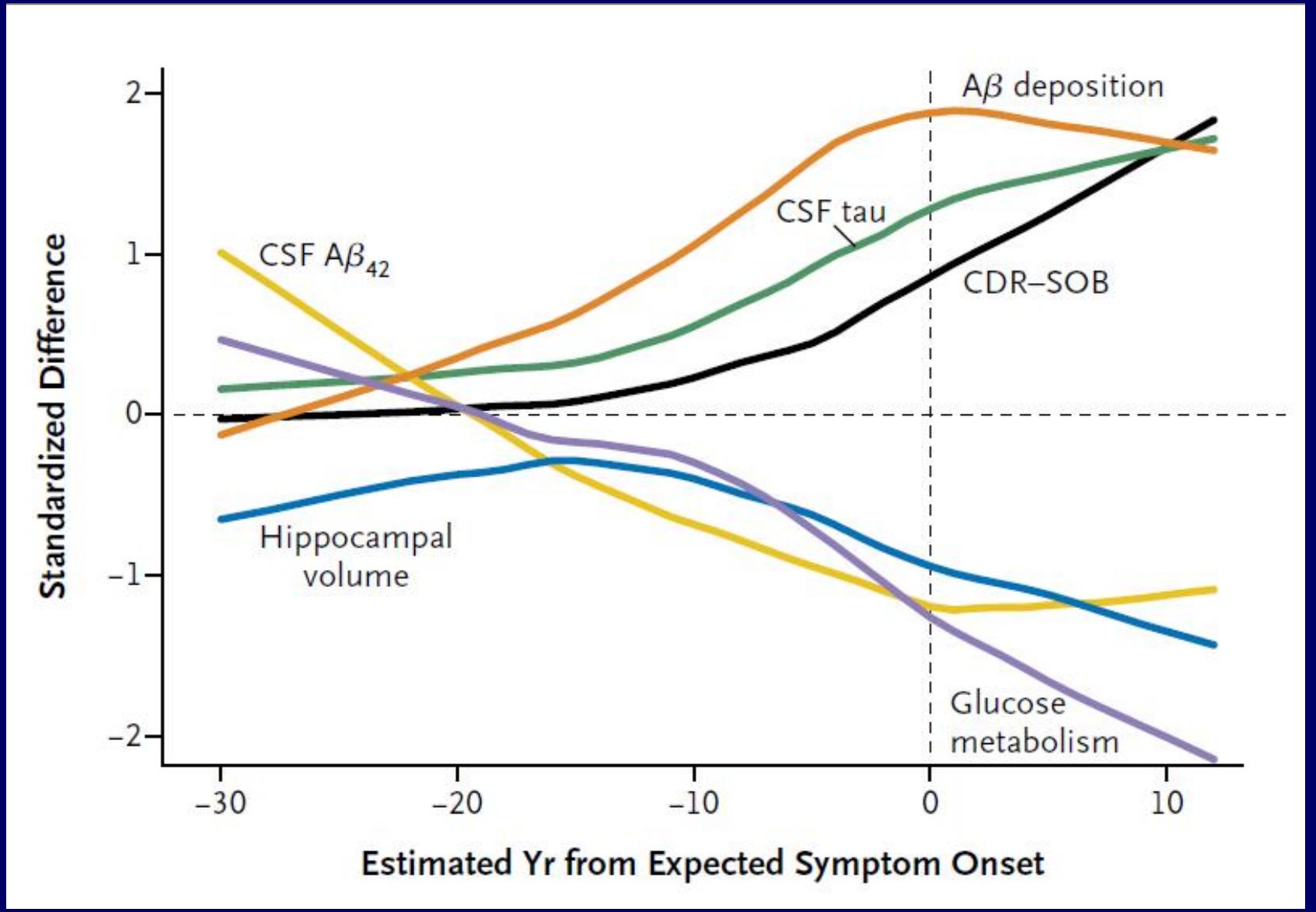
128 subjects:
88 carriers
(40 PSEN1,
3 PSEN2,
8 APP pedigrees)
and 40
noncarriers



Bateman et al., NEJM 2012

NEUROIMAGING IN DEMENTIA

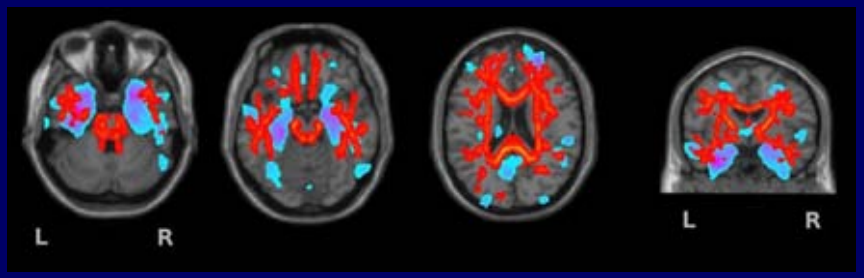
Dominantly inherited AD – Combined model



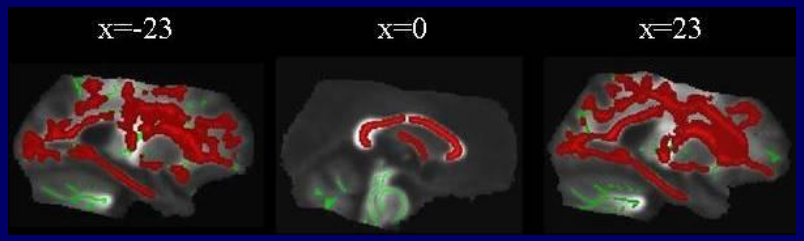
NEUROIMAGING IN DEMENTIA

AD / WM damage

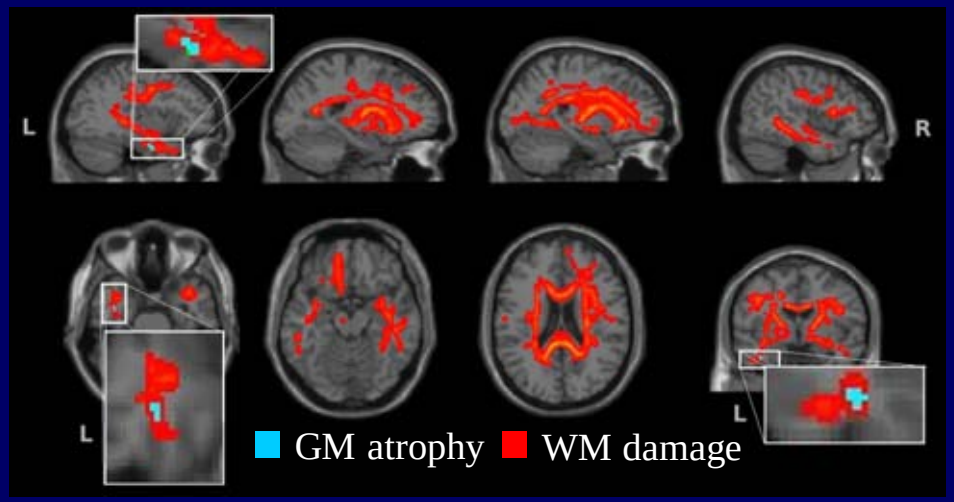
AD



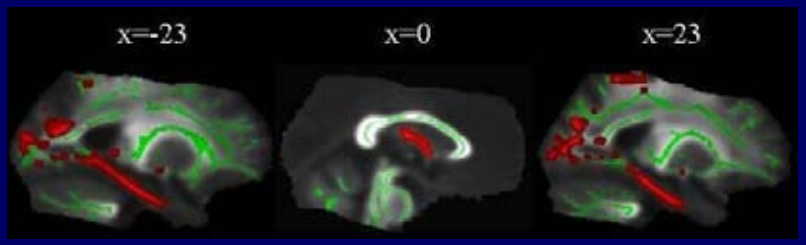
Increased MD



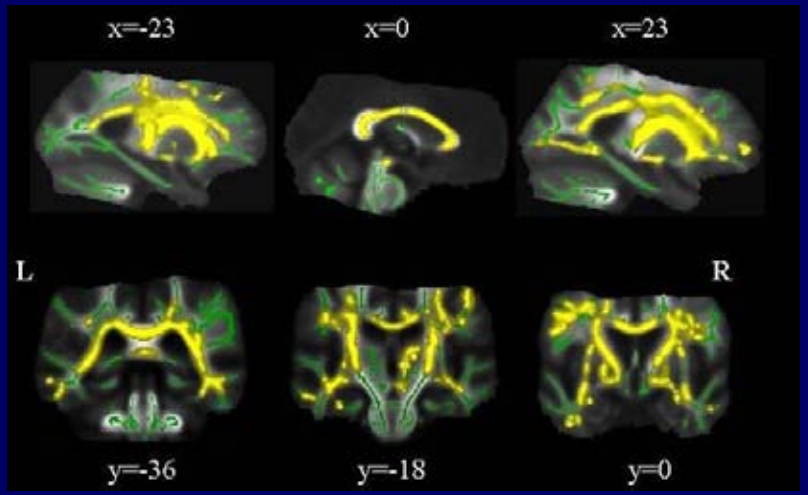
MCI



Decreased FA



MCI: Increased axial D

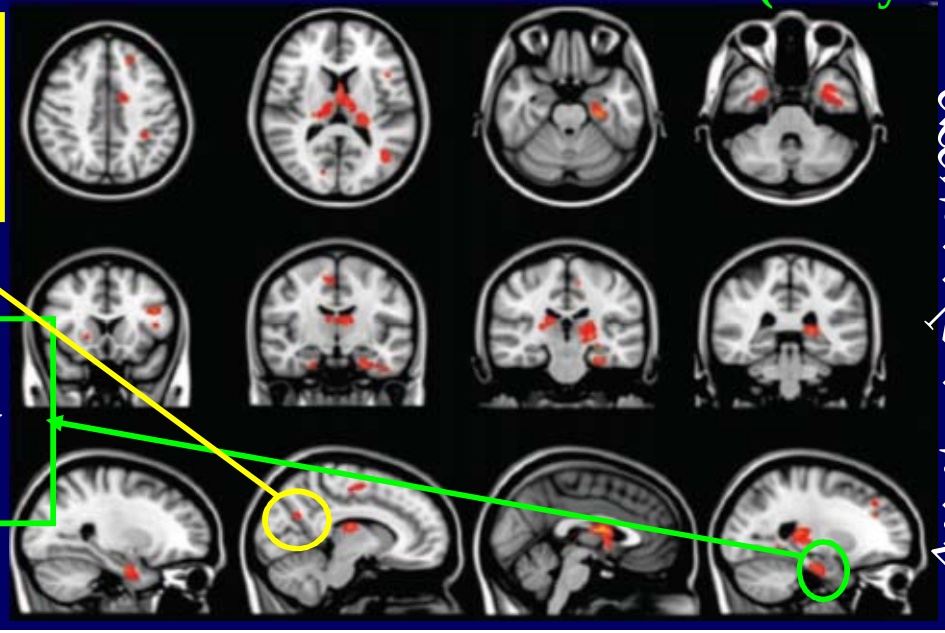


Agosta, … Filippi. Radiology 2011

CN-aMCI converters *vs.* CN-stable (FU 2yrs)

Predictor of convertion to MCI (p=0.01)

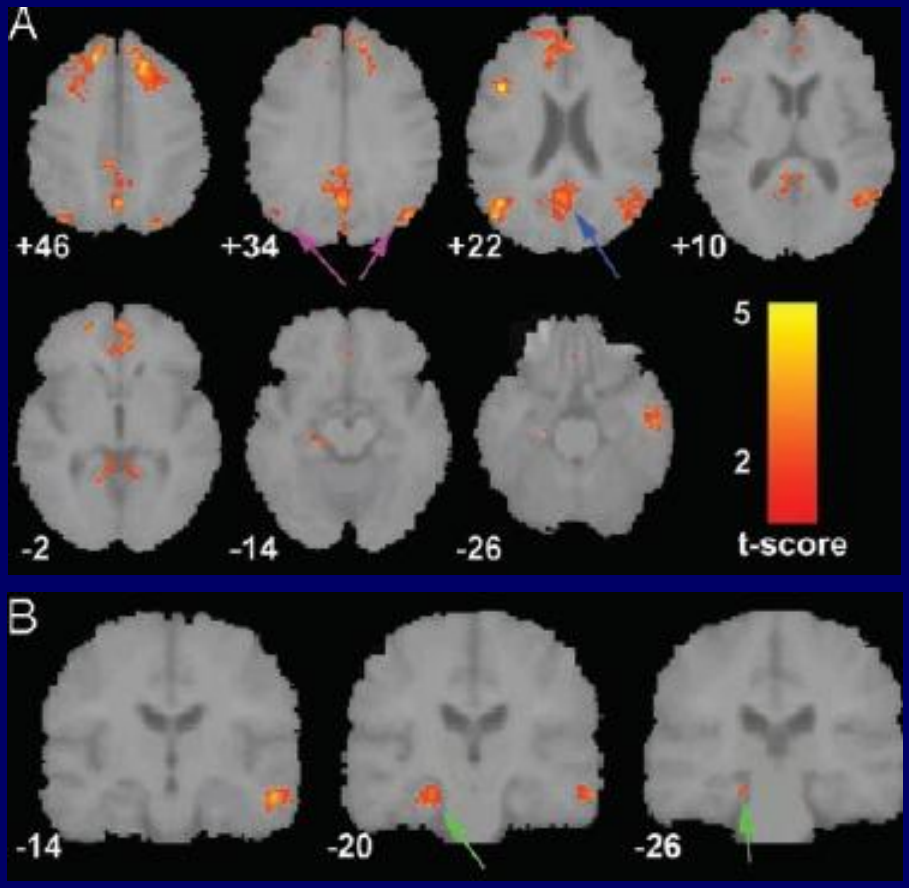
Predictor of episodic memory decline (p=0.03)



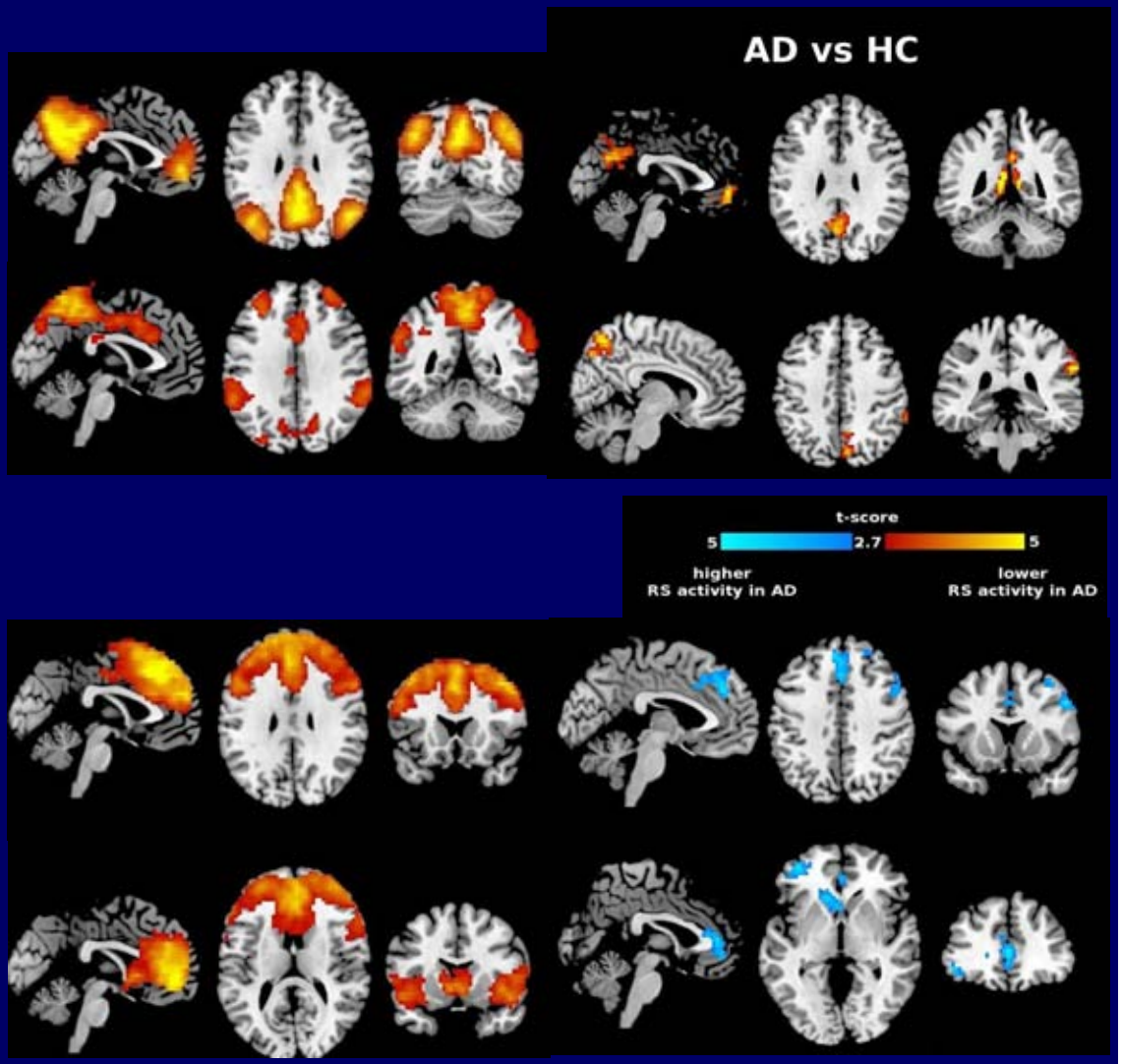
NEUROIMAGING IN DEMENTIA

AD / Cortical reorganization

Decreased network activity in AD patients *vs.* controls



Greicius et al., PNAS 2004

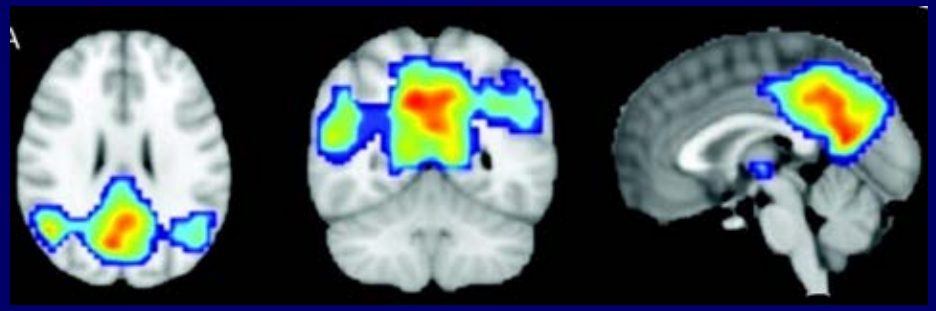


Agosta, … Filippi. Neurobiol Aging 2011

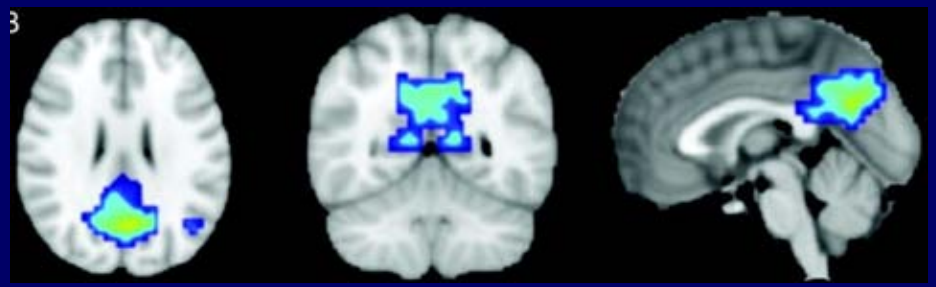
NEUROIMAGING IN DEMENTIA

MCI and normal à AD / Cortical reorganization

MCI nonconverters



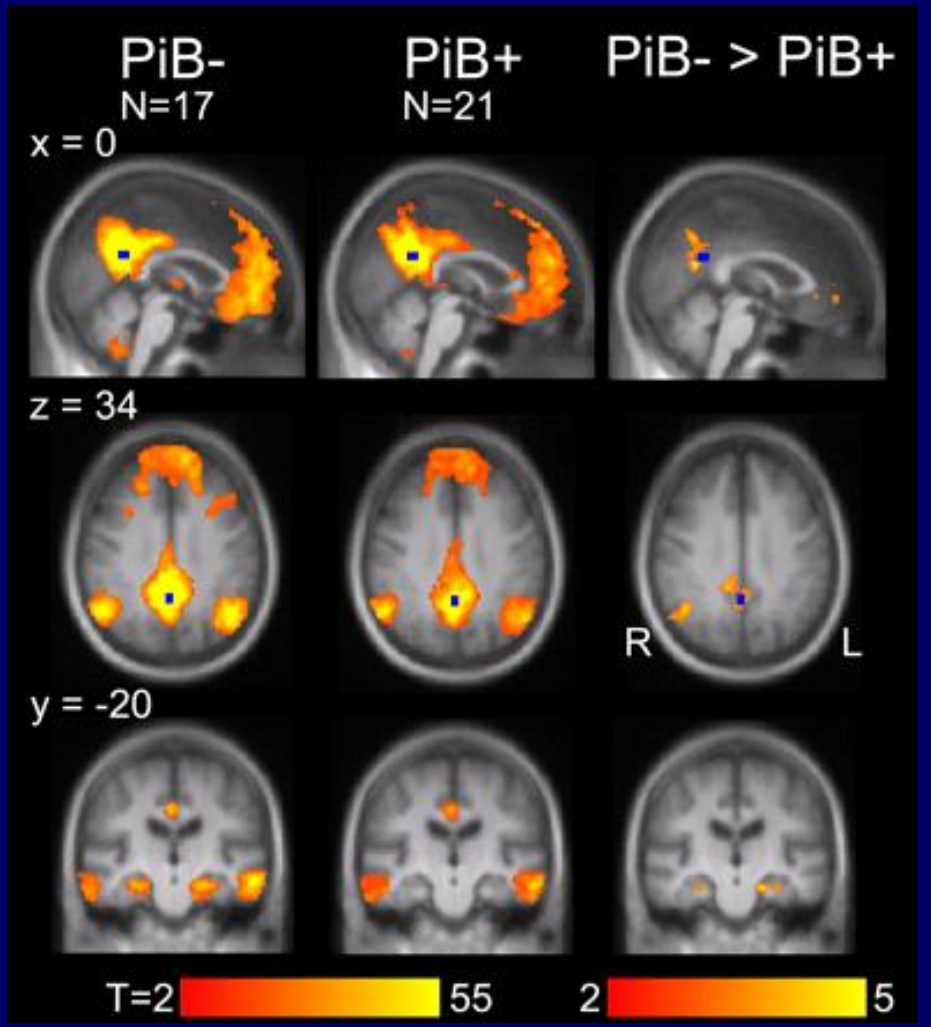
MCI converters



	Cognitive outcome tested in models	
Variables in model	Model 1: conversion to AD	Model 2: D CDR-SB
GOF	10.64 (0.025) [20.16 to 1.12]	−3.84 (0.0075) [−1.23 to −6.44]
DMN-GM	70.75 (0.040) [139.49 to 2.02]	−32.51 (0.0036) [−12.56 to −52.46]
Age	0.07 (0.65) [0.37 to −0.23]	−0.01 (0.83) [0.09 to −0.11]
Education	0.33 (0.29) [0.96 to −0.30]	−0.13 (0.35) [0.14 to −0.41]
MMSE	1.16 (0.053) [2.36 to −0.04]	−0.20 (0.30) [0.18 to −0.59]
CVLT-del	—	—

Rombouts et al., Neurobiol Aging

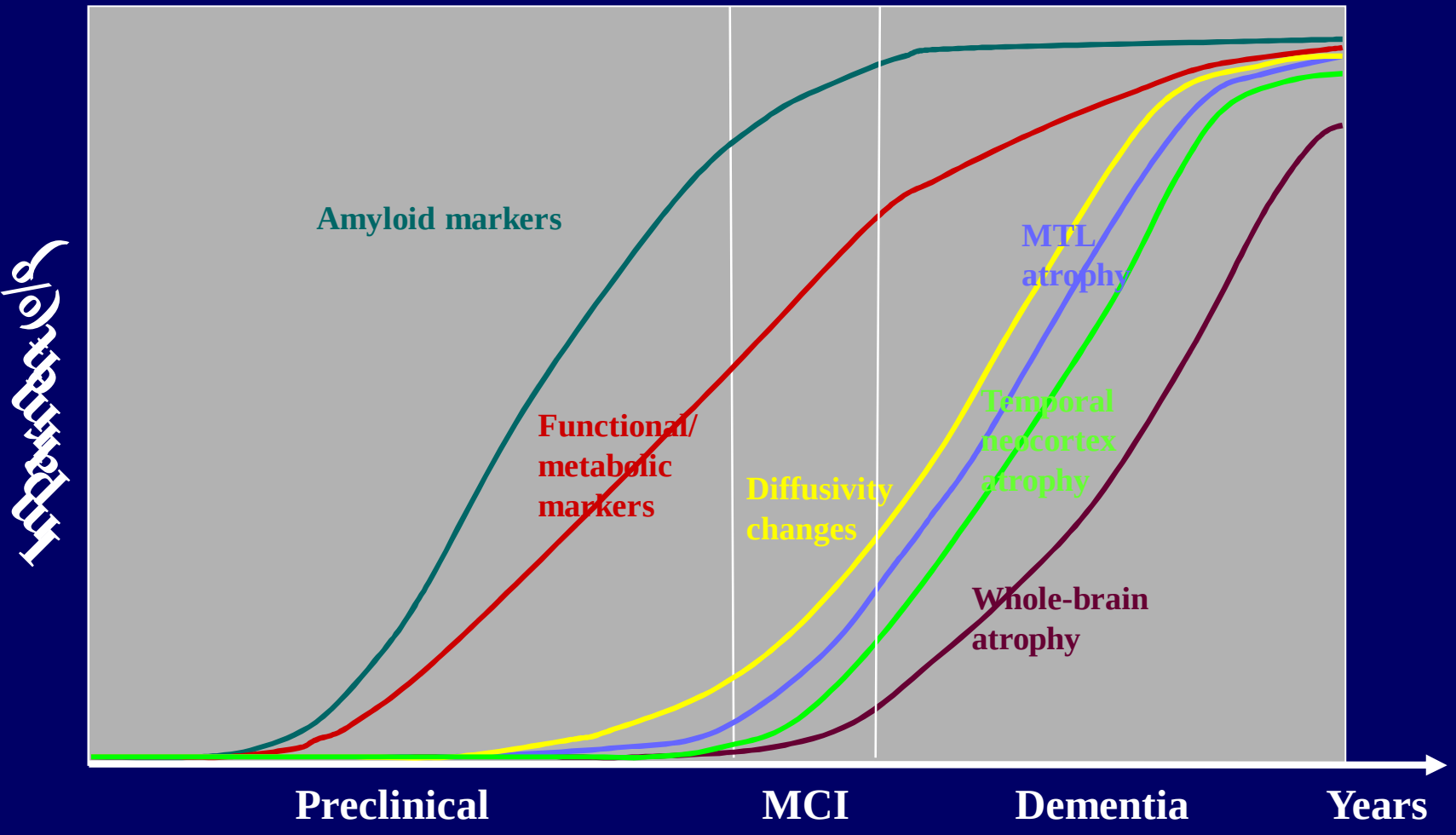
CN PIB+ *vs.* PIB-



Hedden et al., J Neurosci 2009

NEUROIMAGING IN DEMENTIA

Modelling neuroimaging findings in AD



NEUROIMAGING IN DEMENTIA

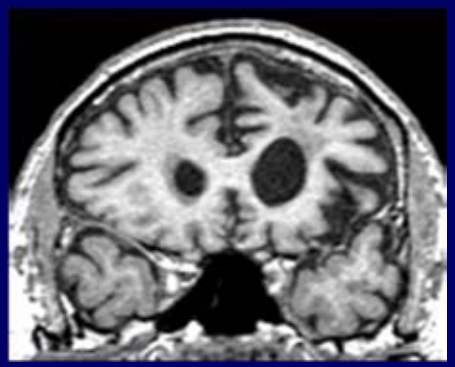
Outline of the presentation

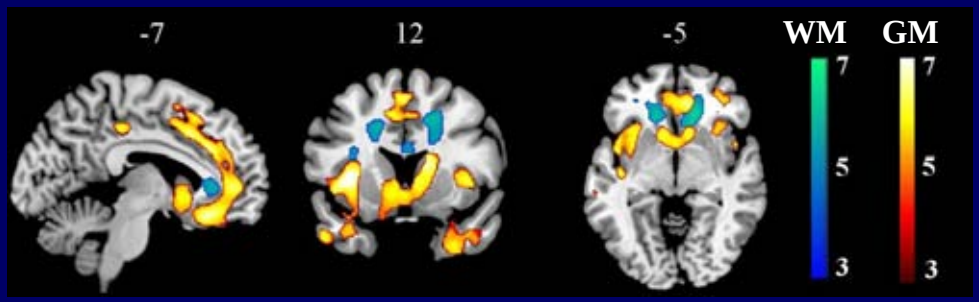
- Alzheimer's disease (AD)
- **Frontotemporal lobar degeneration (FTLD)**

NEUROIMAGING IN DEMENTIA

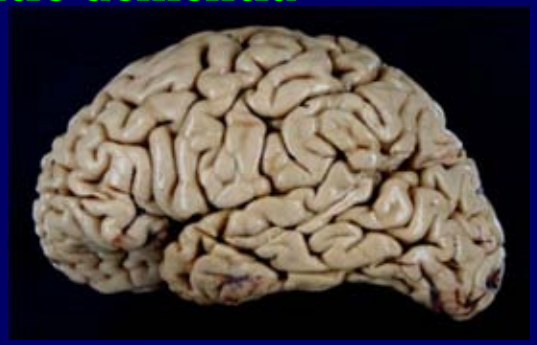
FTLD / Brain atrophy

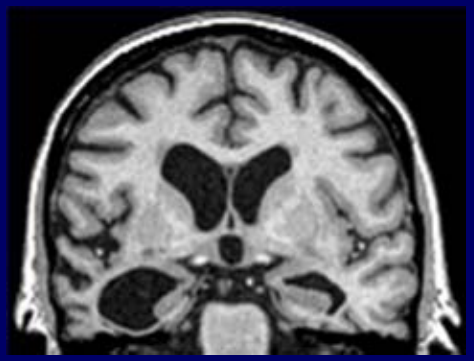
Behavioral FTD

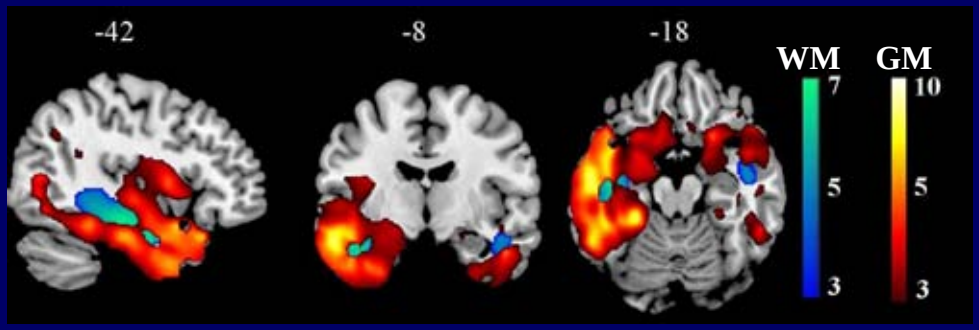




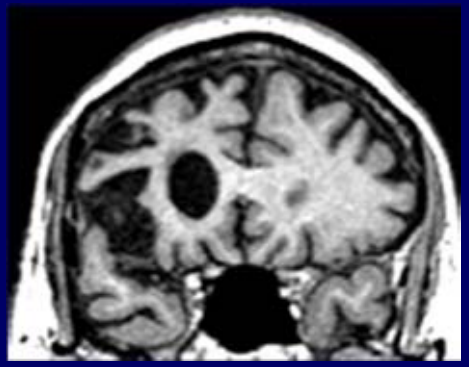
Semantic dementia

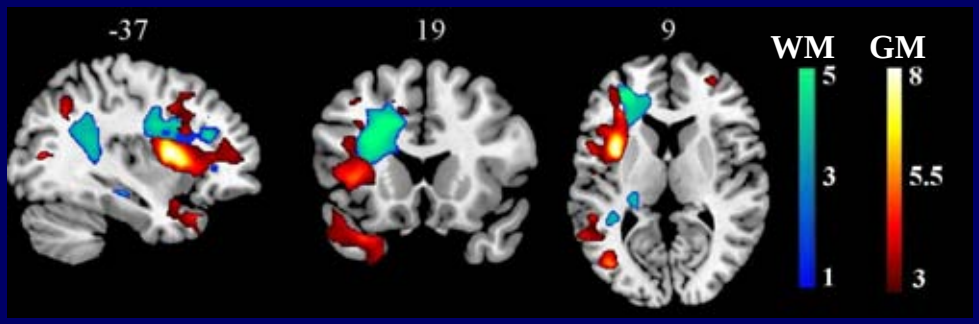






Nonfluent aphasia





Courtesy of M.L. Gorno-Tempini

Agosta, … Filippi. Cer Cortex 2011

NEUROIMAGING IN DEMENTIA

bvFTD and PPA / Revised diagnostic criteria

III. Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria.

- A. Meets criteria for possible bvFTD
- B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
- C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
  - C.1. Frontal and/or anterior temporal atrophy on MRI or CT
  - C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

Rascovsky et al., Brain 2011

Nonfluent

II. Imaging-supported nonfluent/agrammatic variant diagnosis

Both of the following criteria must be present:

1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Imaging must show one or more of the following results:
   a. Predominant left posterior fronto-insular atrophy on MRI or
   b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET

Semantic

II. Imaging-supported semantic variant PPA diagnosis

Both of the following criteria must be present:

1. Clinical diagnosis of semantic variant PPA
2. Imaging must show one or more of the following results:
   a. Predominant anterior temporal lobe atrophy
   b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

Logopenic

II. Imaging-supported logopenic variant diagnosis

Both criteria must be present:

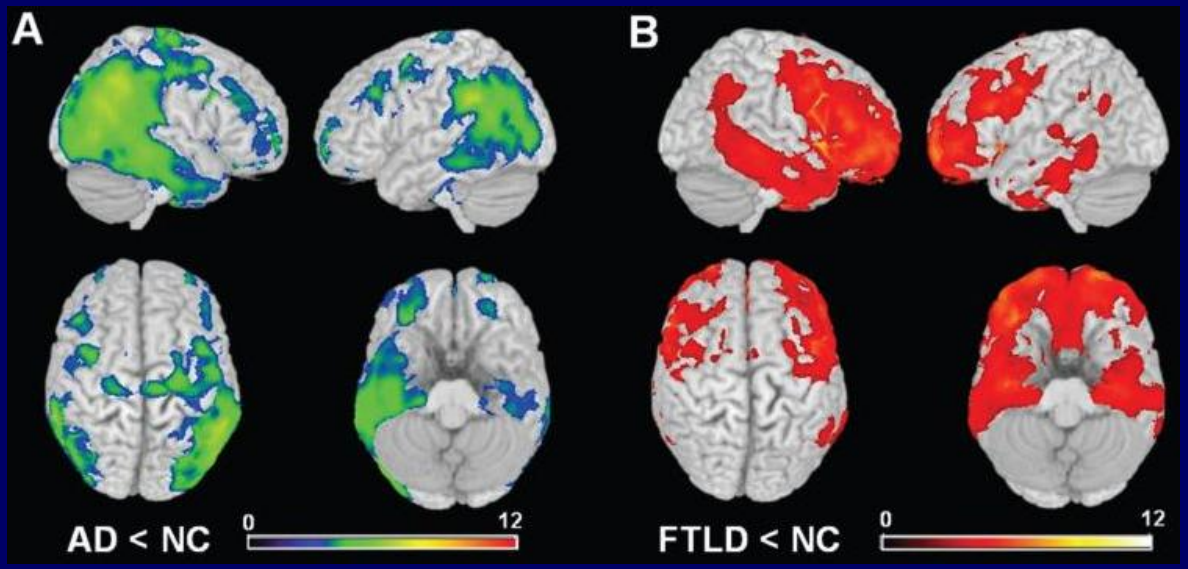
1. Clinical diagnosis of logopenic variant PPA
2. Imaging must show at least one of the following results:
   a. Predominant left posterior perisylvian or parietal atrophy on MRI
   b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET

Gorno-Tempini et al., Neurology 2011

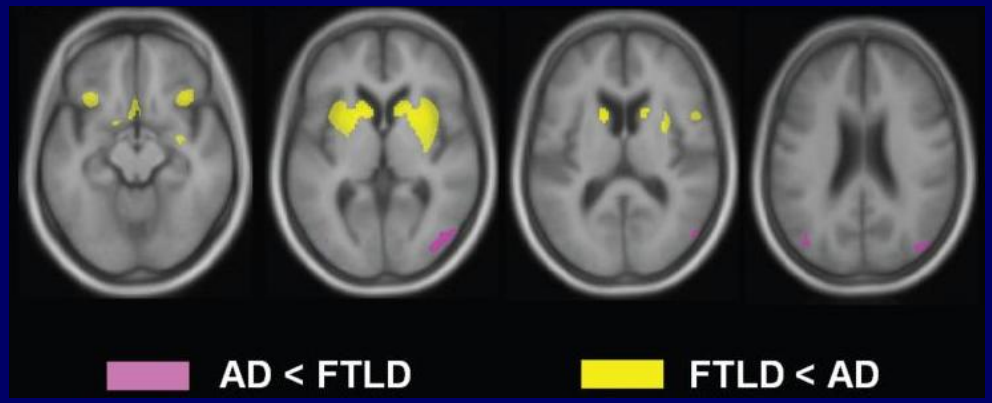
NEUROIMAGING IN DEMENTIA

FTLD *vs.* AD / Brain atrophy and metabolism

AD *vs.* controls **BvFTD *vs.* controls**

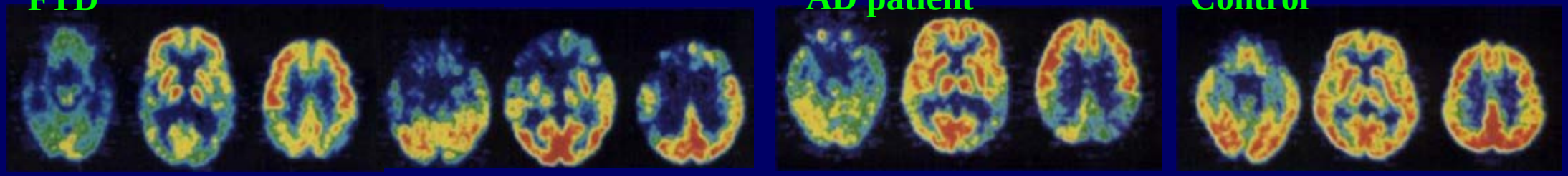


bvFTD *vs.* AD



Rabinovici et al., Am J Alzheimer's Dis Ass Disorders 2008

FTD **AD patient** **Control**



Ishii et al., J Nucl Med 1998

Table 5 Diagnostic accuracy, sensitivity and specificity

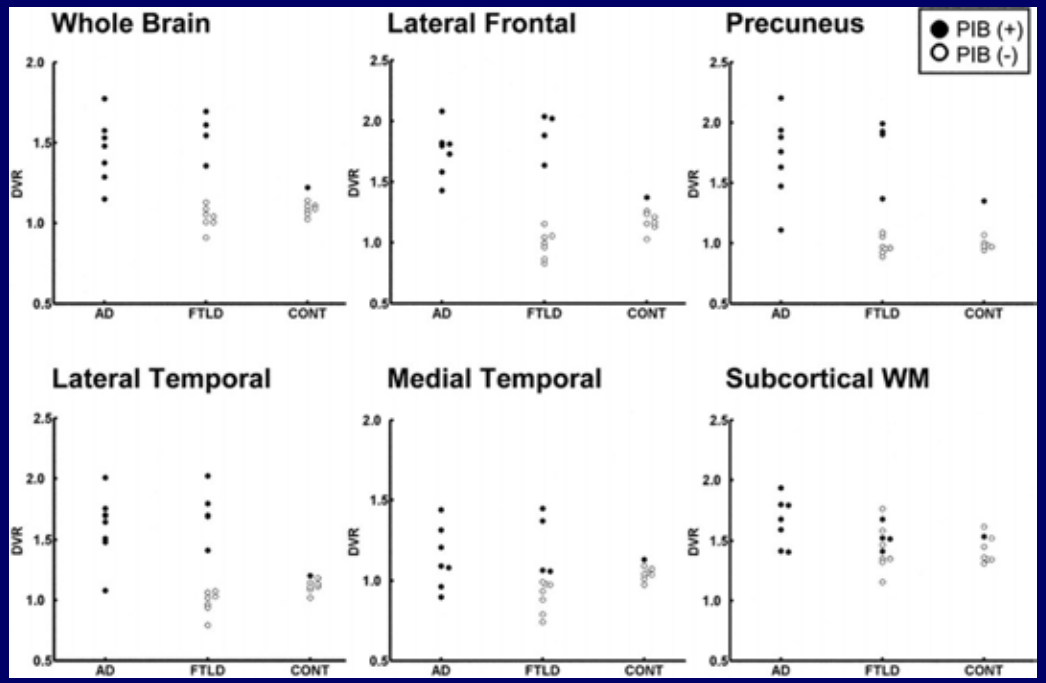
	Clinical scenario	Symptom checklist	Scenario + checklist	Transaxial FDG-PET	SSP FDG-PET
Mean FTD specificity/AD sensitivity	86% (74–100)	94% (74–100)	88% (74–100)	96% (92–100)	97.6% (94–100)

Foster et al., Brain 2007

NEUROIMAGING IN DEMENTIA

FTLD *vs* AD / Amyloid imaging

PIB PET in FTLD

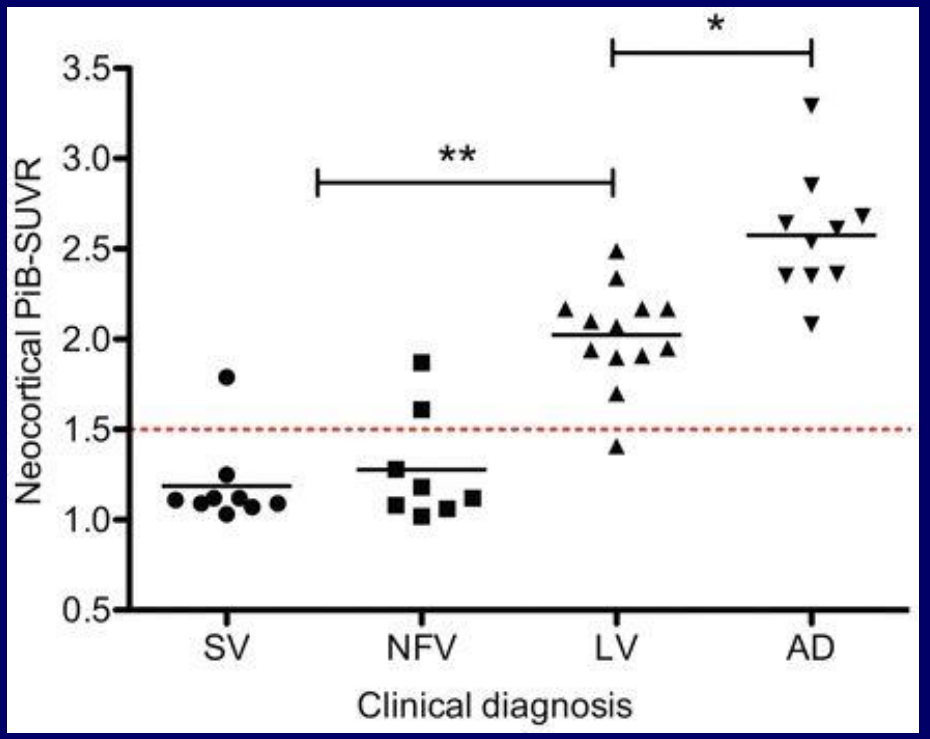


FTLD did not differ from controls

PIB higher in AD than in FTLD in whole brain, lateral frontal, precuneus, and lateral temporal cortex

Rabinovici et al., Neurology 2007

PIB PET in PPA



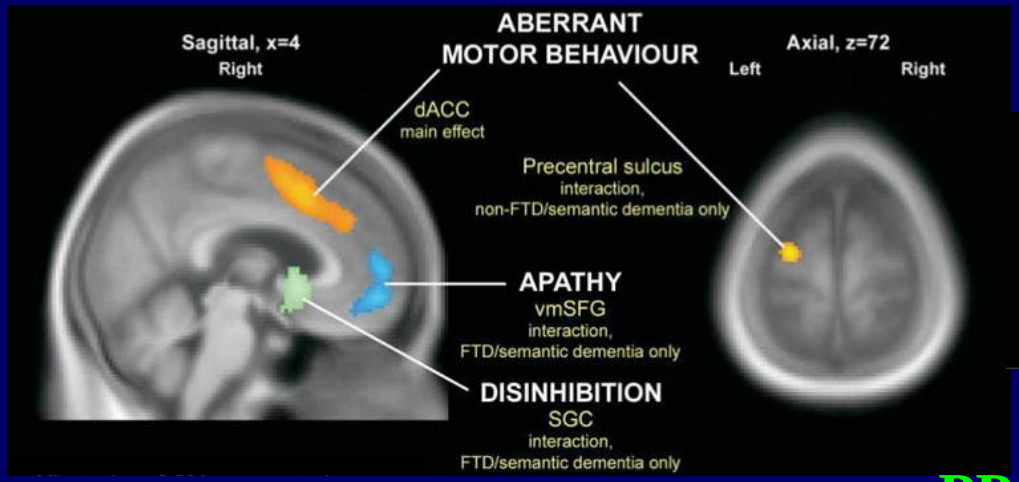
Positive PiB amyloid uptake:
12 /13 logopenic (92%)
1/9 semantic (11%)
2/8 nonfluent (25%)

Leyton et al., Brain 2011

NEUROIMAGING IN DEMENTIA

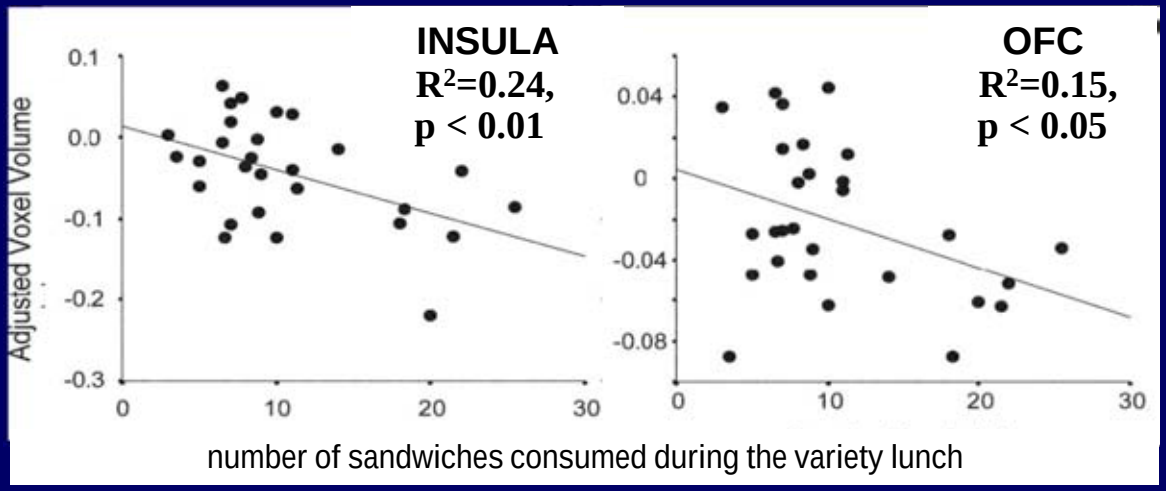
FTLD / Atrophy *vs* behavioral and language changes

bvFTD: NPI sub-domains *vs.* GM atrophy



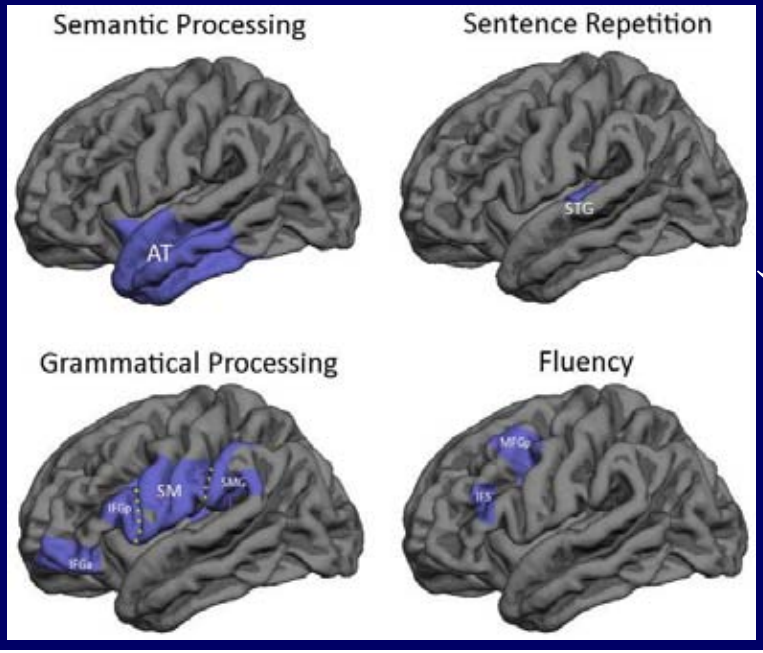
Rosen et al., Brain 2005

bvFTD: abnormal eating behaviors *vs.* GM loss



Woolley et al., Neurology 2007

PPA: cortical thickness *vs.* language features

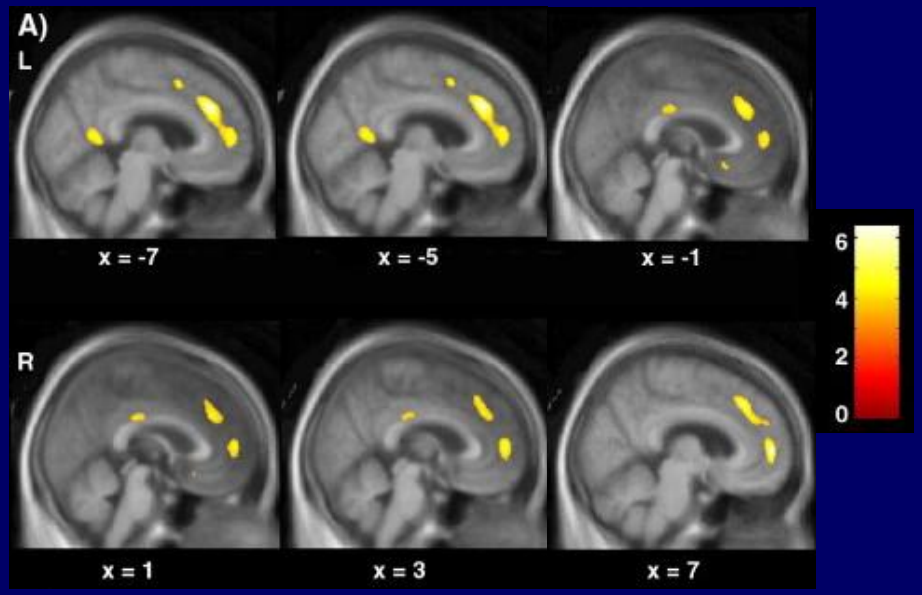


Rogalski et al., Neurology 2011

NEUROIMAGING IN DEMENTIA

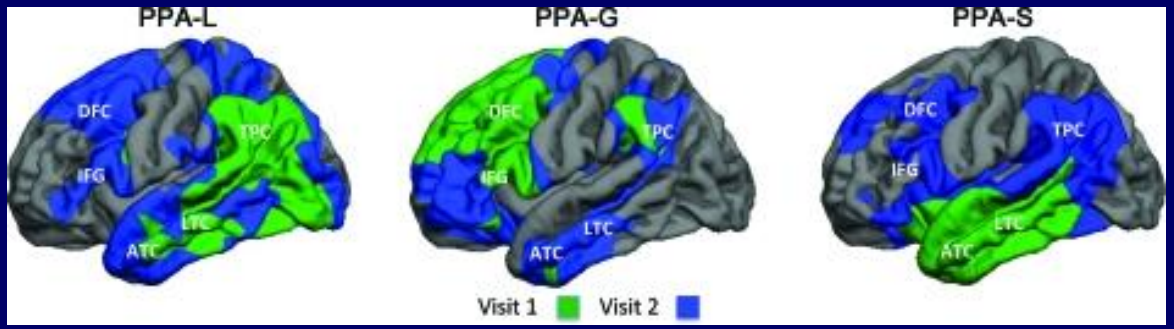
FTLD / Atrophy progression

GM atrophy progression over 1 year in bvFTD



Brambati et al., NeuroImage 2007

GM atrophy progression over 2 years in PPA



Rogalski et al., Neurology 2011

Rates of 1-y whole brain atrophy *vs.* behavioral and cognitive changes

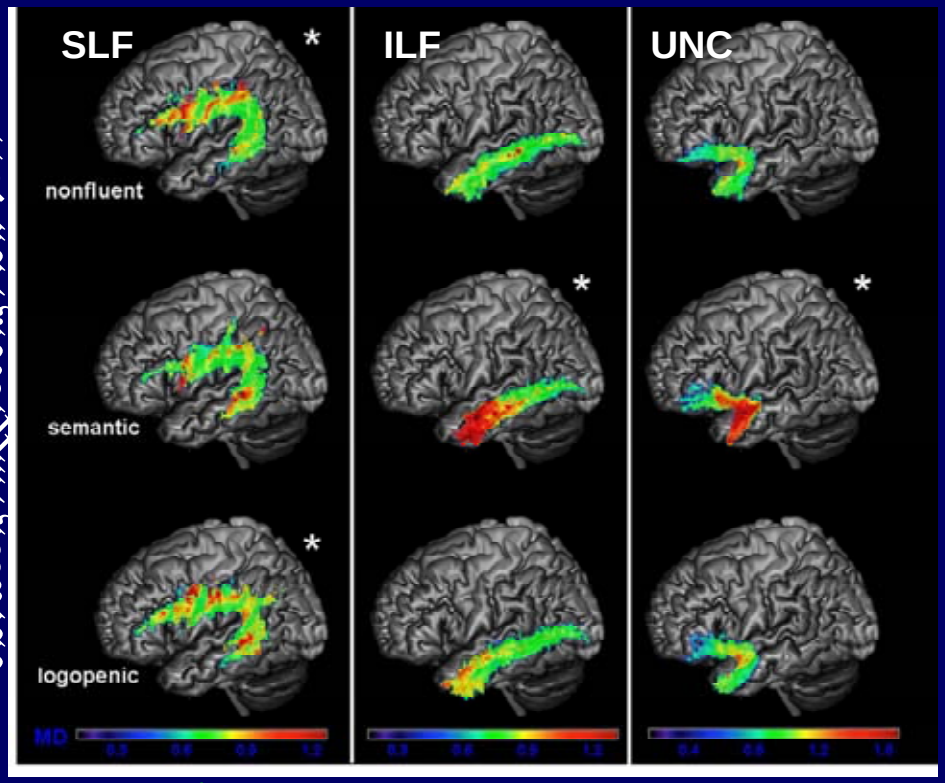
	Increase in annual whole brain atrophy (%) (95% CI)[a]	*p* Value
MMSE change		
FTLD cohort	0.3 (0.2 to 0.4)	<0.001[b]
bvFTD	0.2 (0.0 to 0.4)	0.05
SemD	0.1 (−2.0 to 2.1)	0.8
PNFA	0.0 (−1.0 to 1.0)	0.9
FAB change		
FTLD cohort	0.3 (0.1 to 0.5)	0.005[b]
bvFTD	0.2 (−7.0 to 7.0)	0.7
SemD	1.0 (−10.6 to 11.4)	0.5
PNFA	0.1 (−0.3 to 0.5)	0.3
CDR-SB change		
FTLD cohort	0.5 (0.2 to 0.7)	0.001[b]
bvFTD	0.3 (−2.4 to 3.0)	0.04[b]
SemD	0.2 (−2.9 to 3.1)	0.6
PNFA	0.3 (0.0 to 0.7)	0.09
NPI-D change		
FTLD cohort	0.0 (0.0 to 0.1)	0.5
bvFTD	0.0 (−0.1 to 0.2)	0.5
SemD	0.2 (−0.1 to 0.5)	0.1
PNFA	0.0 (−0.4 to 0.5)	0.7

Cardenas, Neurology 2013

NEUROIMAGING IN DEMENTIA

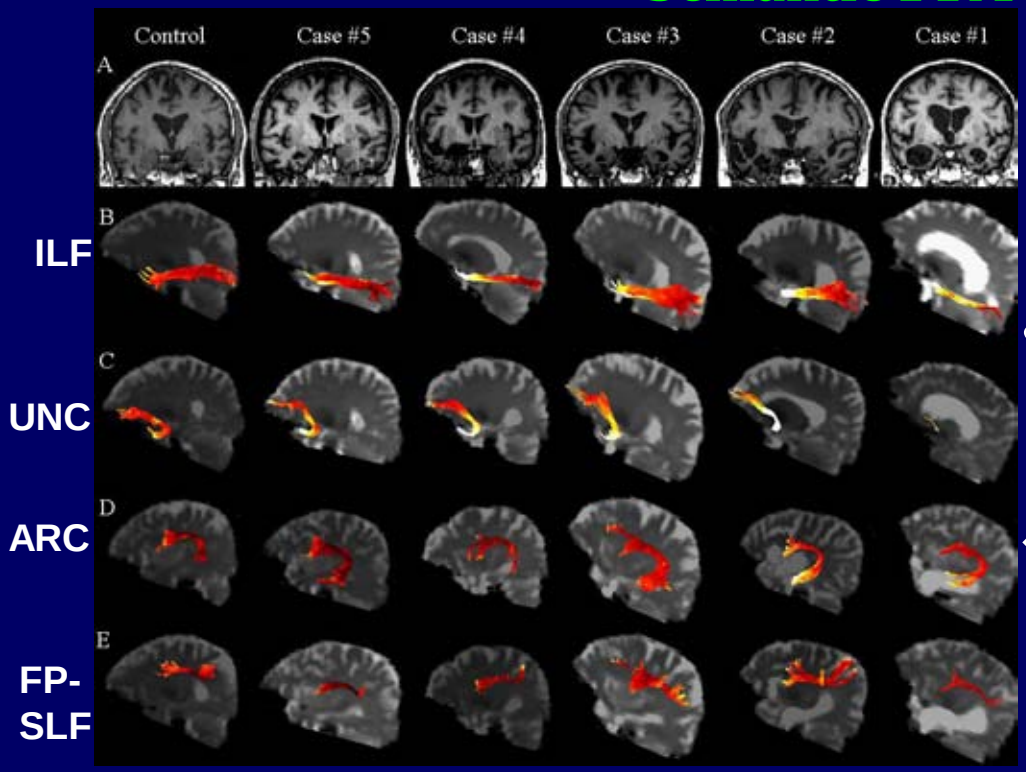
FTLD / WM damage

PPA variants



Mesulam, Brain 2001; 124: 2169

Semantic PPA



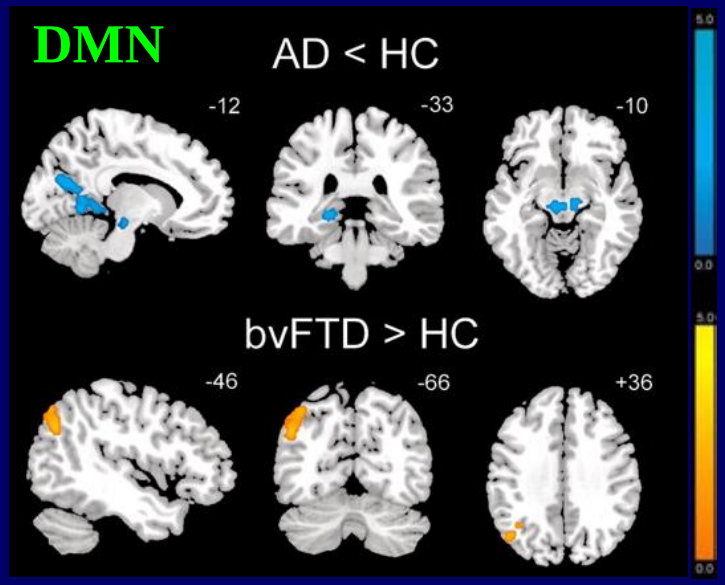
Agosta, Neurology 2010; 74: 1530

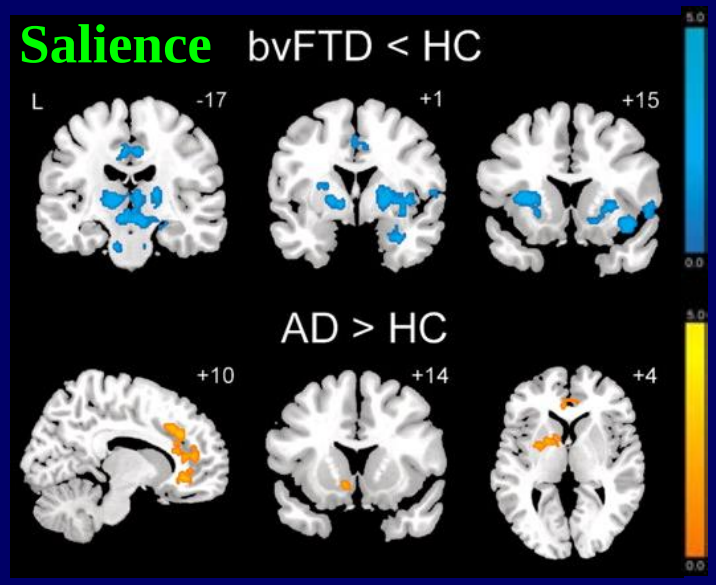
Patient groups comparison	Ranking of variable importance	Mean decrease in accuracy	C index
bvFTD *vs.* nonfluent	L SLF radD	1.00	0.74
	Anterior CC radD	0.97	0.74
bvFTD *vs.* semantic	L ILF axD	1.00	0.91
	L uncinate axD	0.57	0.88
Nonfluent *vs.* semantic	L uncinate axD	1.00	0.96
	L ILF axD	0.93	0.98

Agosta, Neurology 2011; 76: 1492

NEUROIMAGING IN DEMENTIA

FTLD *vs* AD / Cortical reorganization

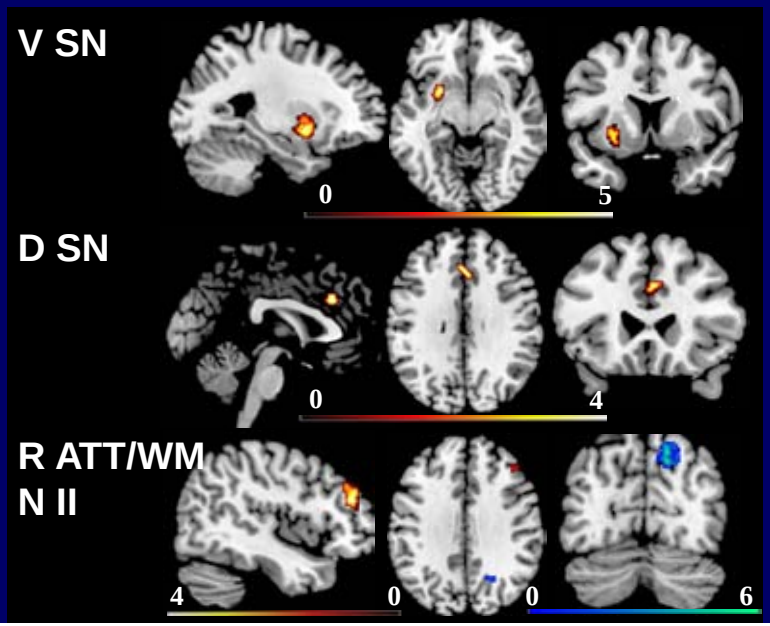




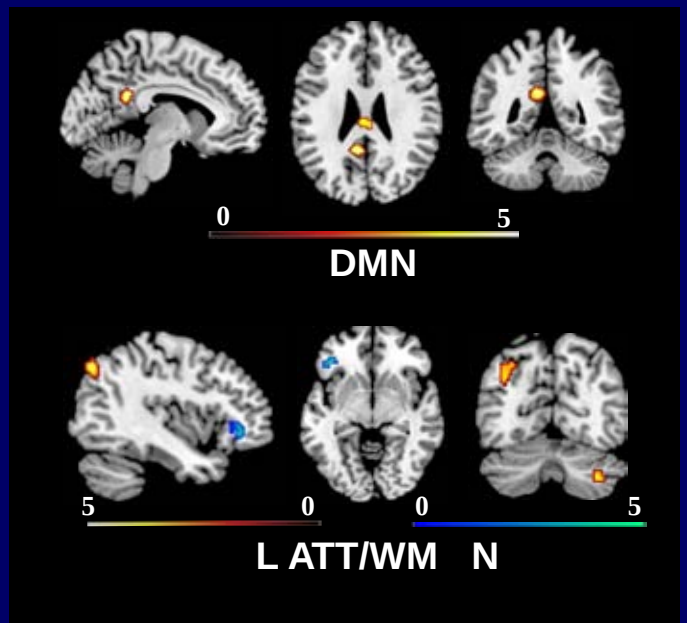
Salience N - DMN score: sensitivity 92%, specificity 96%

Zhou et al., Brain 2010

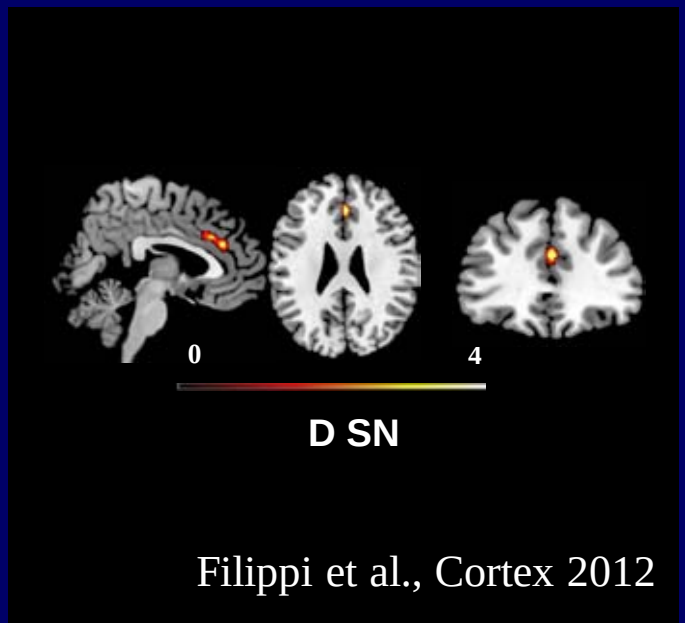
bvFTD *vs.* HC



AD *vs.* HC



bvFTD *vs.* AD

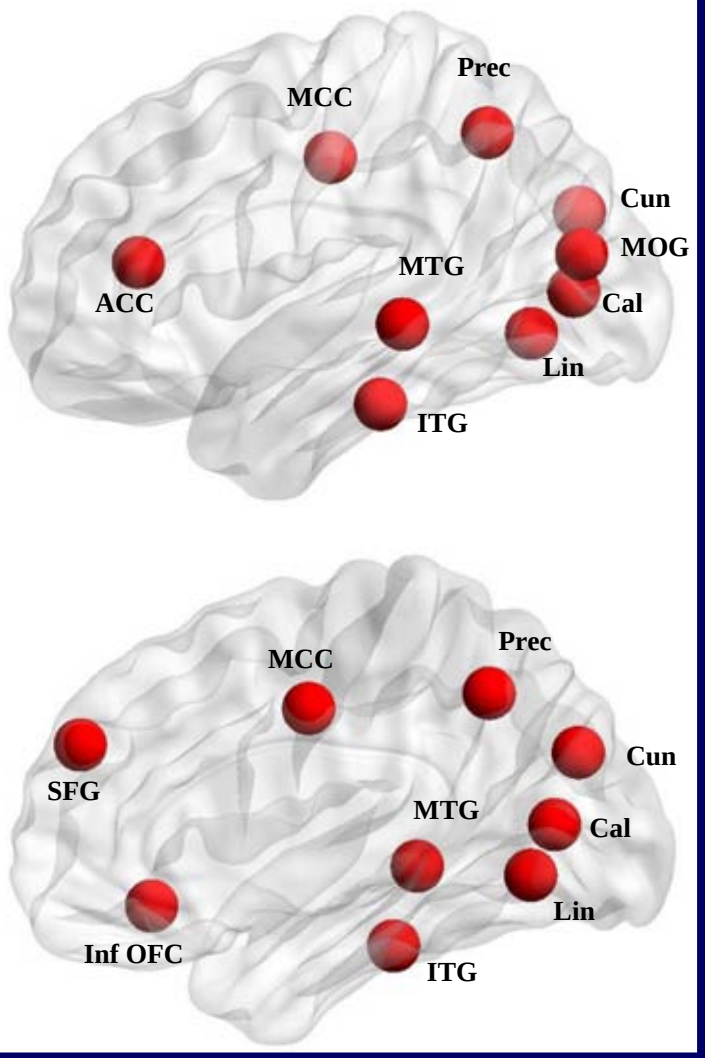


Filippi et al., Cortex 2012

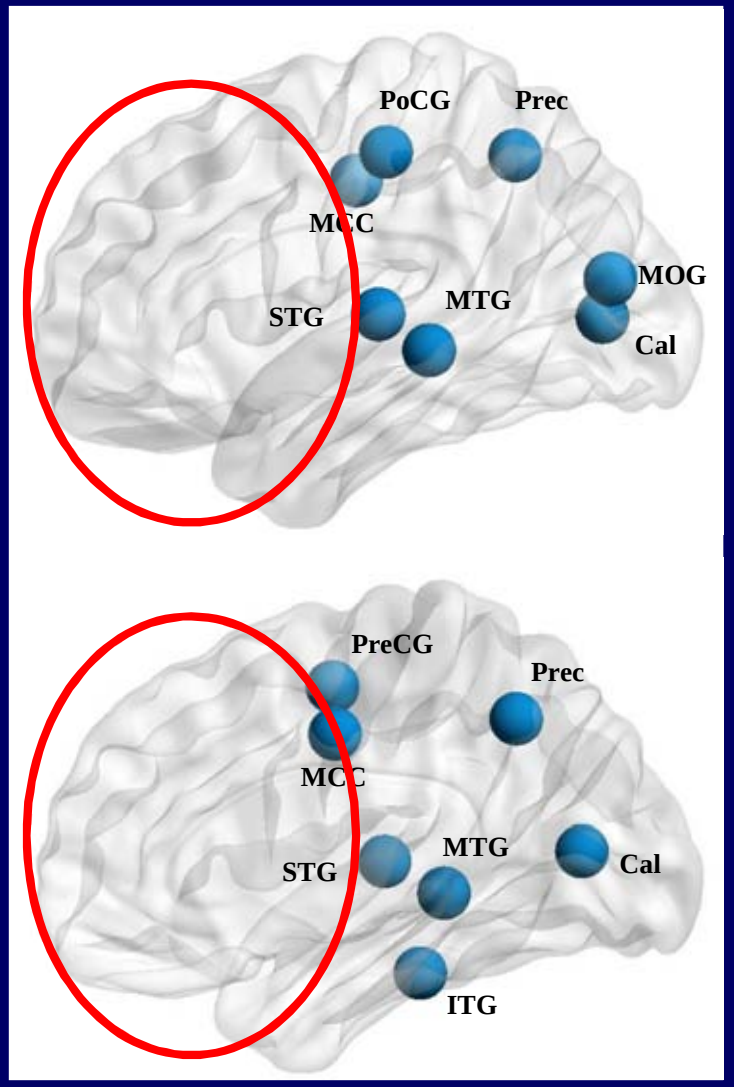
NEUROIMAGING IN DEMENTIA

bvFTD / Graph analysis

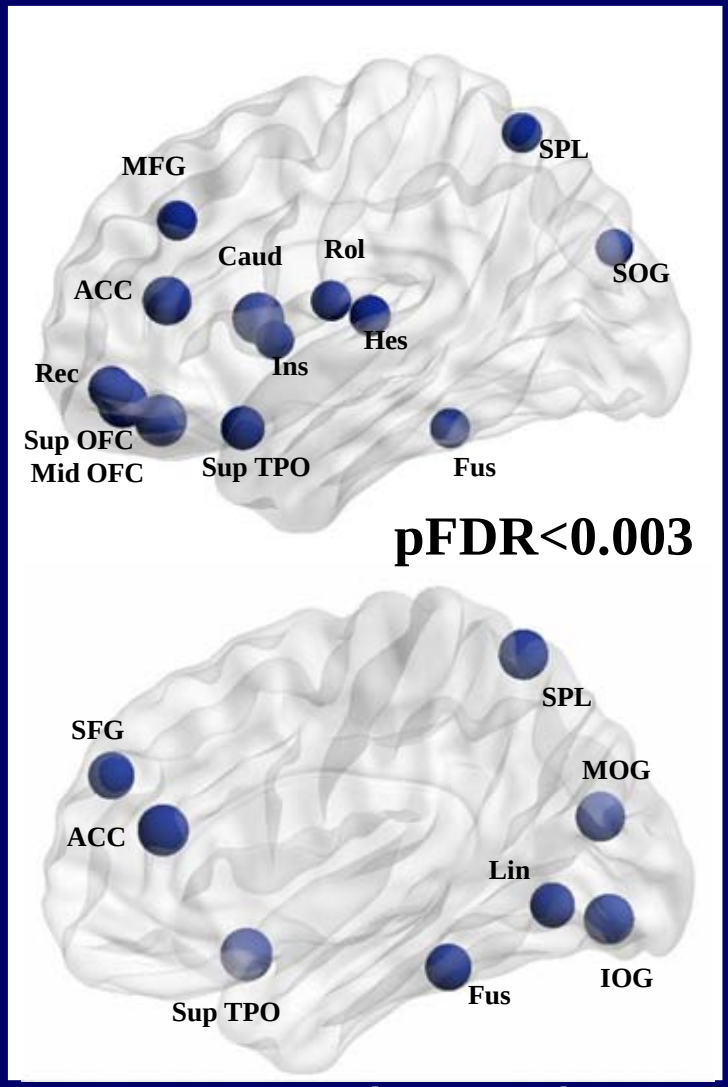
Cortical hubs: healthy controls



Cortical hubs: bvFTD



Reduced nodal degree: bvFTD *vs* controls



pFDR<0.003

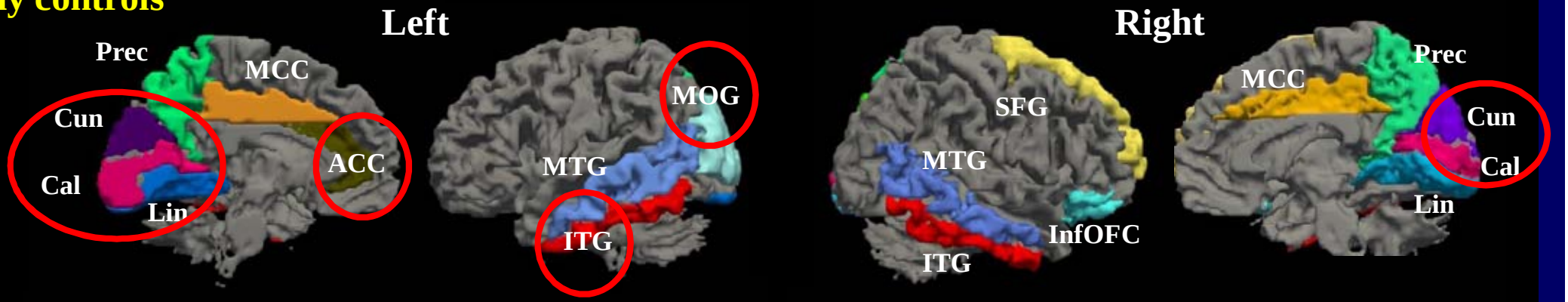
Agosta, ... Filippi. Neurology 2013

NEUROIMAGING IN DEMENTIA

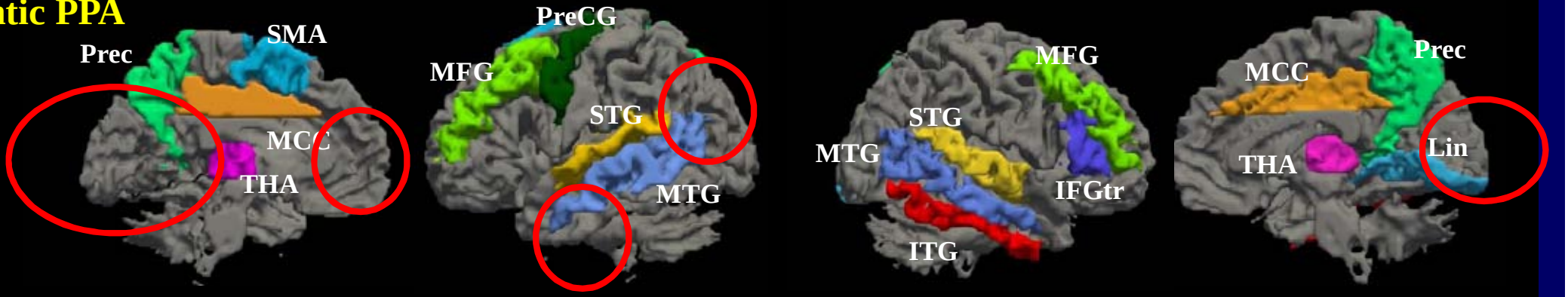
Cortical hubs

Semantic PPA/ Graph analysis

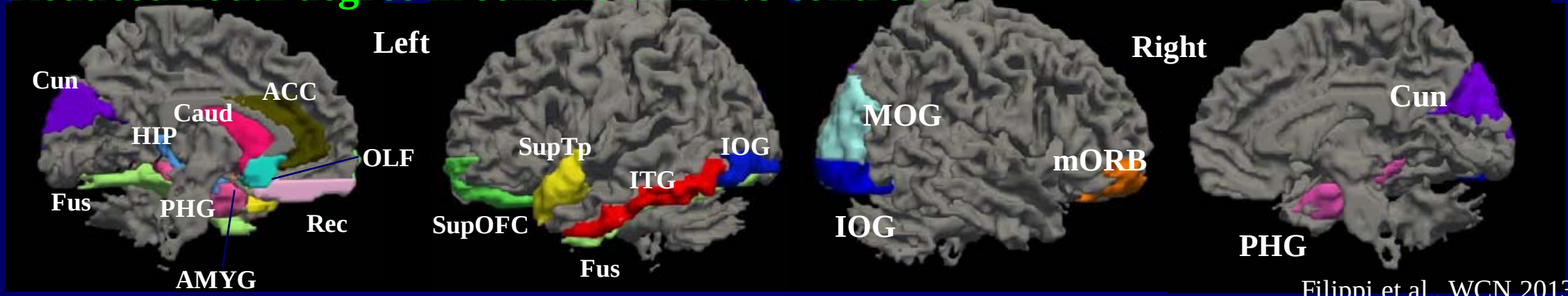
Healthy controls



Semantic PPA



Reduced nodal degree in semantic PPA *vs* controls

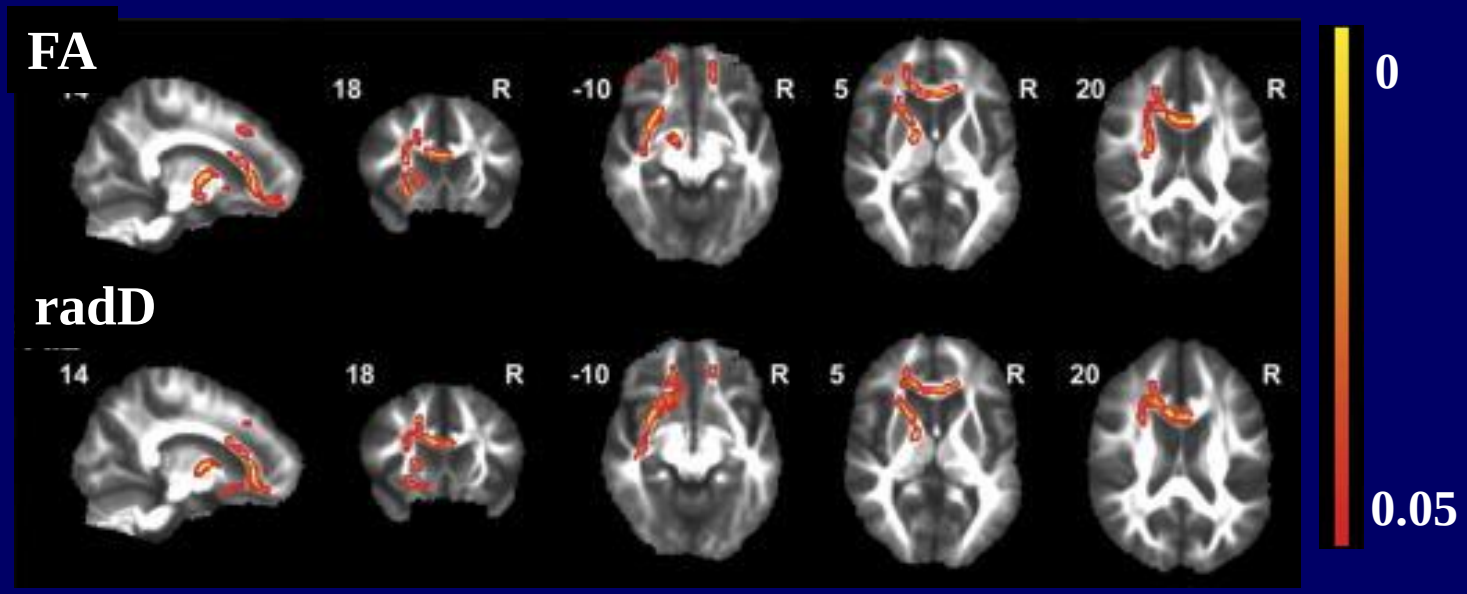


Filippi et al., WCN 2013

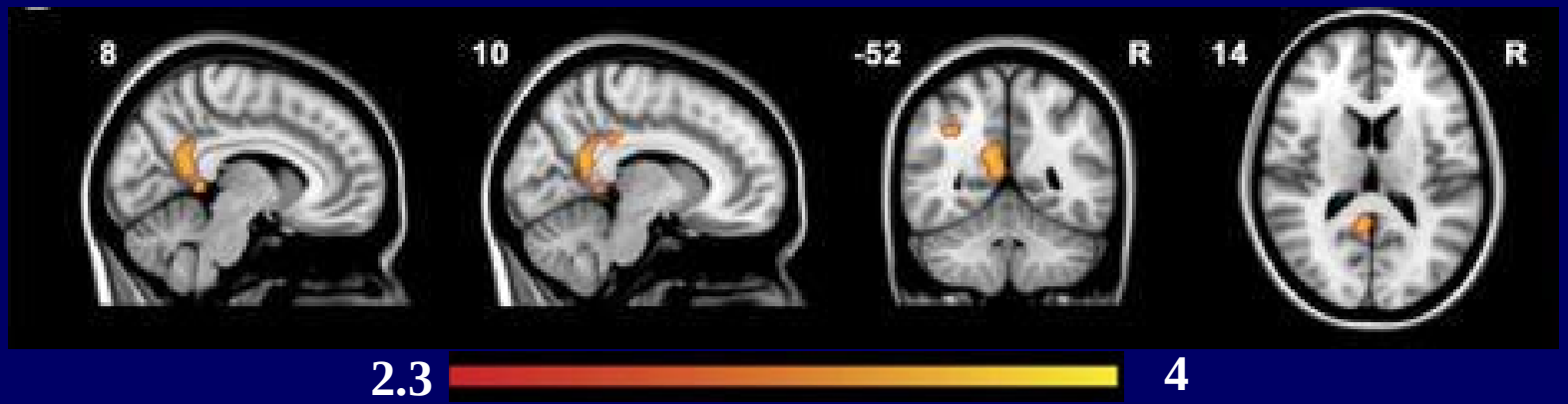
NEUROIMAGING IN DEMENTIA

FTLD / Asymptomatic GRN and MAPT mutation carriers

WM damage

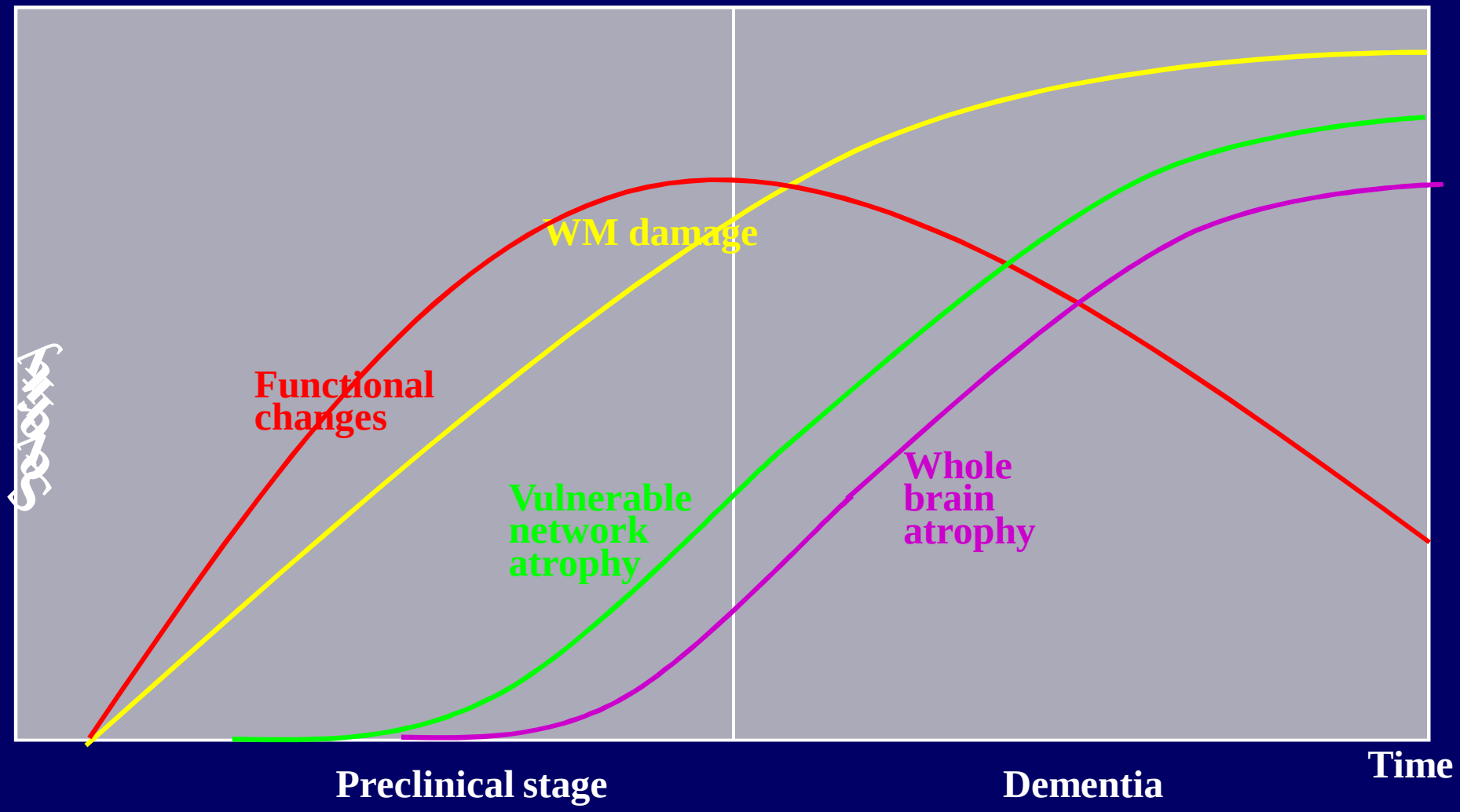


Decreased anterior midcingulate functional connectivity



NEUROIMAGING IN DEMENTIA

Modelling neuroimaging findings in FTLD



NEUROIMAGING IN DEMENTIA

Conclusions

- **The ability of imaging techniques to characterize dementing conditions and to contribute to the diagnostic work-up is improved notably in the last few years.**
- **A multimodal approach, such as one that combines neuropsychological testing, MRI and PET, might improve the classification of these patients from disease onset.**
- **Several structural and functional correlates of cognitive and behavioral deficits in patients with dementia have been described.**
- **Longitudinal studies are needed to understand the dynamics of structural and functional changes on the evolution of cognitive and behavioral abnormalities in these conditions.**

DIVISION OF NEUROSCIENCE

BRAINMAP
Human BRAin IN-vivo MAPping with neuroimaging

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