ACCELERATING THE PACE OF CHANGE

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Contribution of MRI for early diagnosis of dementia

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OSPEDALE SAN RAFFAELE

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2) Section Editor of *NeuroImage: Clinical*
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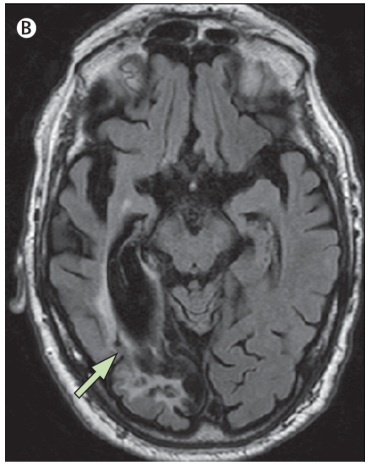
MRI IN DEMENTIA

Exclusion of other causes

Vascular cognitive impairment

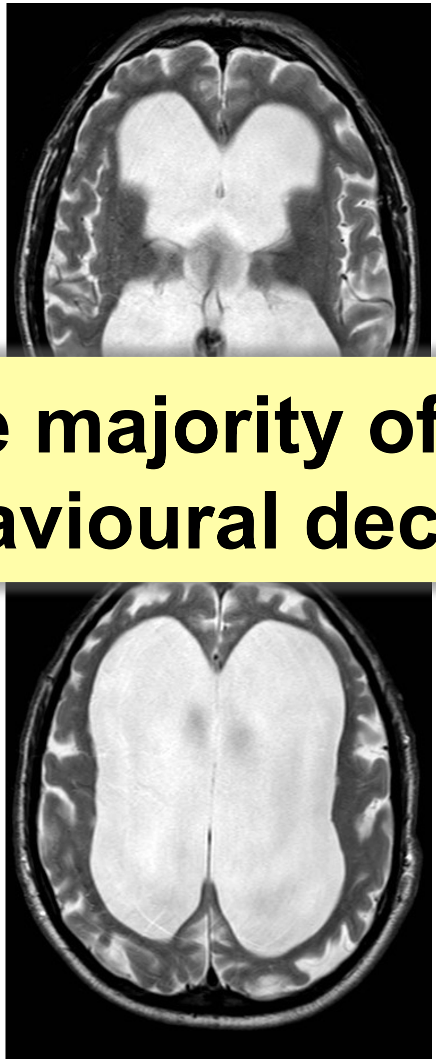


Multiple lacunar infarcts

Extensive (>25%) WM lesions

O'Brien and Thomas, Lancet Neurol 2015

Normal pressure hydrocephalus

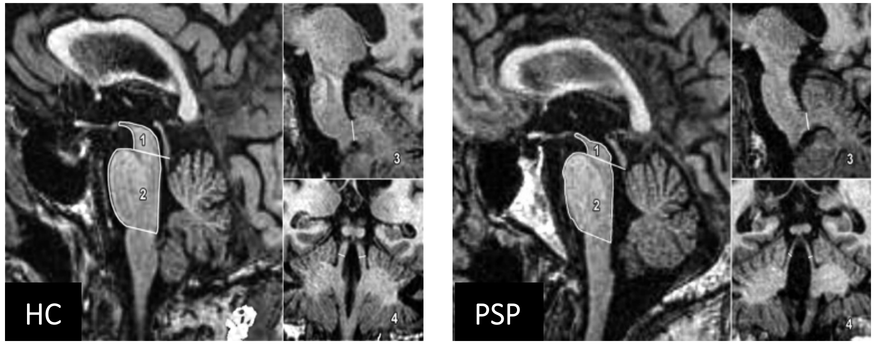


Atypical parkinsonisms

Cutoff and Statistical Values	MR Parkinsonism Index Value	MCP/SCP Value	P/M Value
PSP patients vs PD patients			
Cutoff value	≥13.55	≥2.69	≥4.88
Sensitivity (%)	100	78.8	90.9
Specificity (%)	100	88.9	93.5
PPV (%)	100	68.4	81.1
PSP patients vs MSA-P patients			
Cutoff value	≥12.85	≥2.43	≥4.62
Sensitivity (%)	100	93.9	97.0
Specificity (%)	100	89.5	94.7

Quattrone et al., Radiology 2008

You will have MRI for the majority of subjects with cognitive/ behavioural decline!



Index: [(P/M) * (MCP/SCP)]

MRI IN DEMENTIA

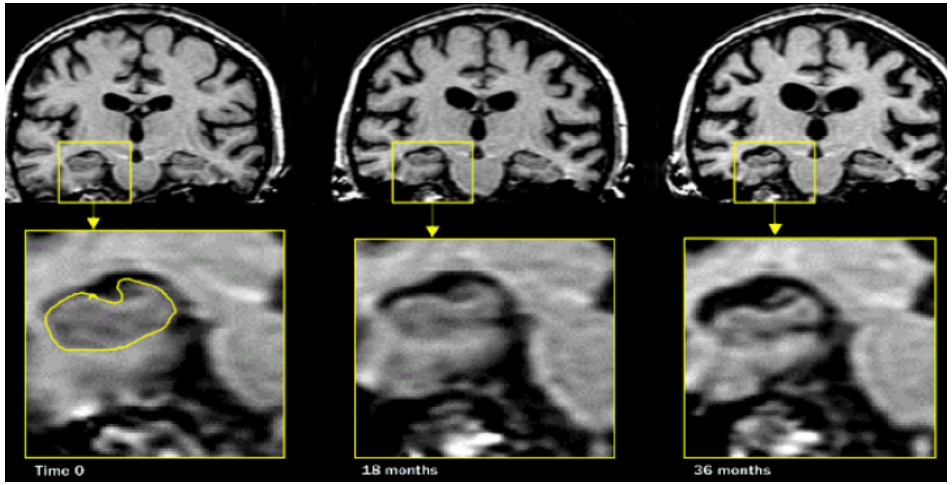
Outline

- **Structural MRI features of the main neurodegenerative dementia (AD *vs* FTD *vs* DLB)**
- Critical issues in the use of MRI in clinical practice
- Any contribution of other MR techniques (DTI and resting state fMRI)?

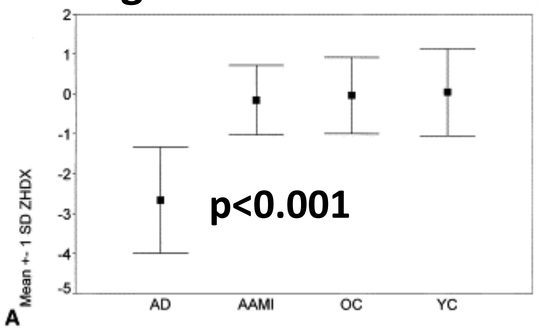
MRI IN DEMENTIA

Brain atrophy in AD

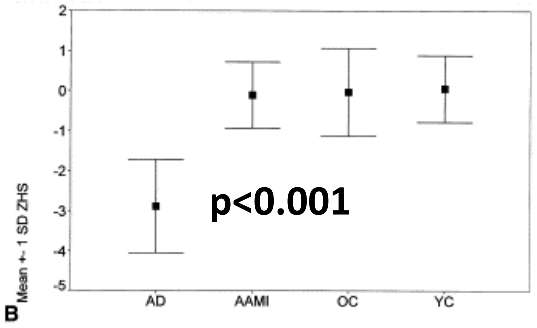
Hippocampal atrophy



Right HV



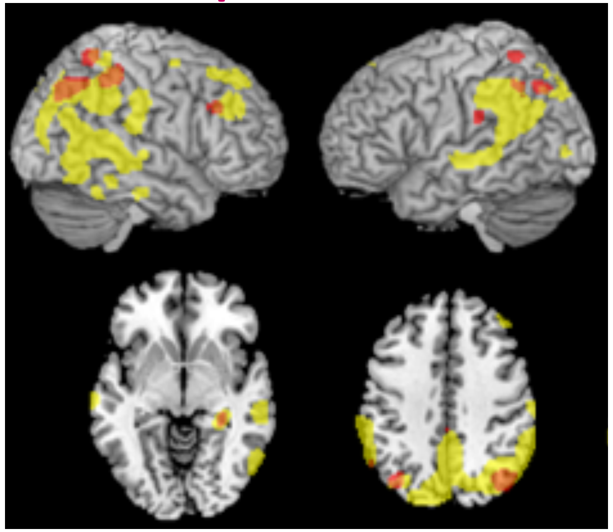
Left HV



Sensitivity 84%, specificity 89%

Laakso et al., Neurobiol Aging 1998

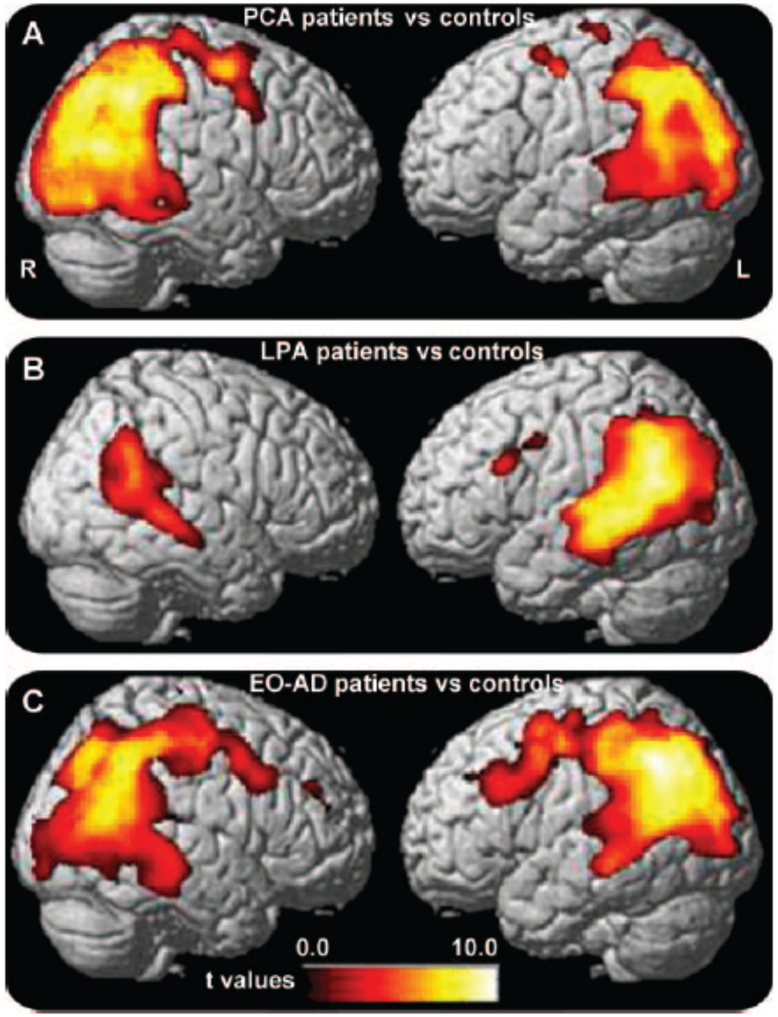
ApoE4 effect



All AD ApoE ε4 carriers *vs* noncarriers

Agosta et al., PNAS 2009

Atypical AD

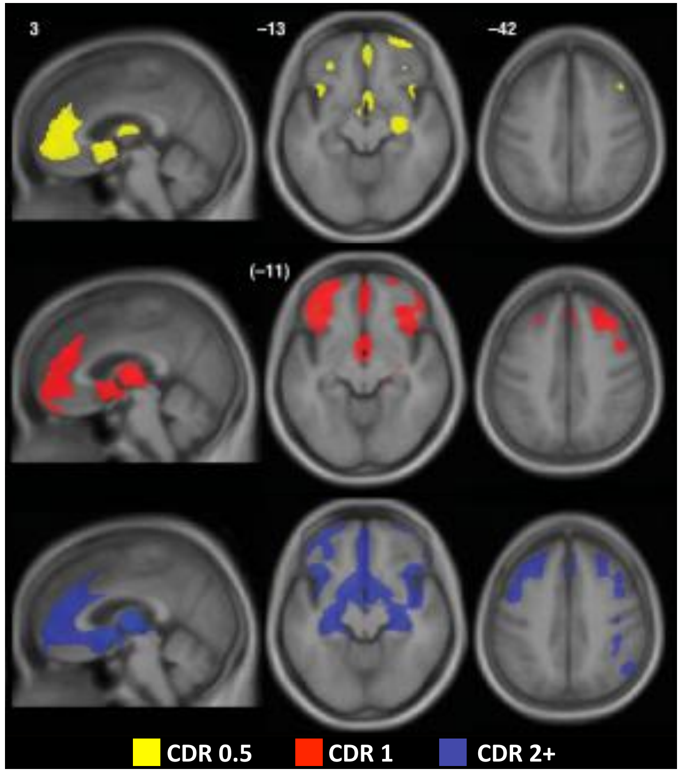


Migliaccio et al., Neurology 2010

MRI IN DEMENTIA

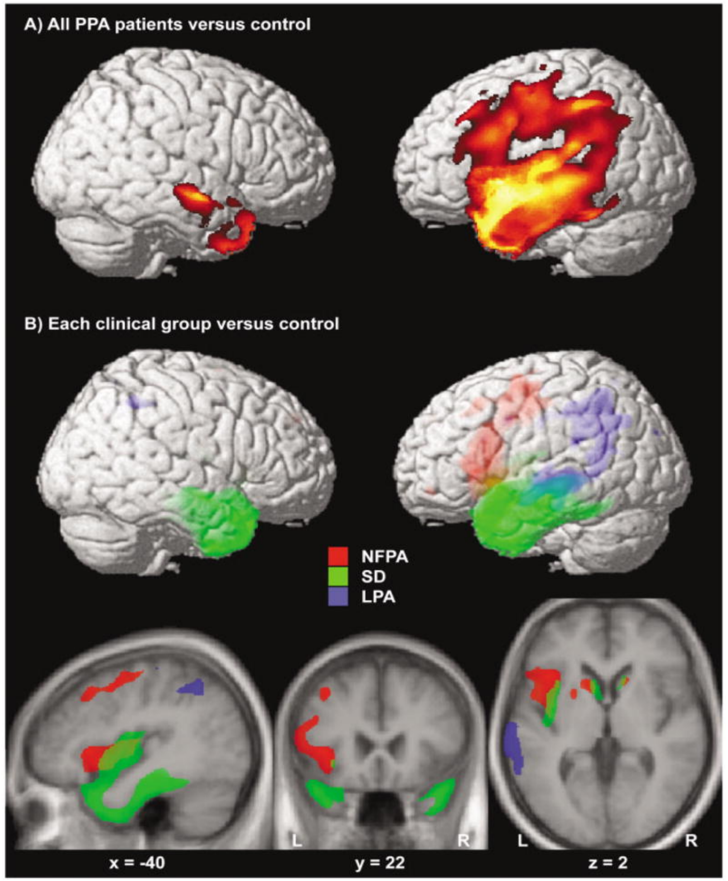
Brain atrophy in non-AD dementia

Behavioural FTD

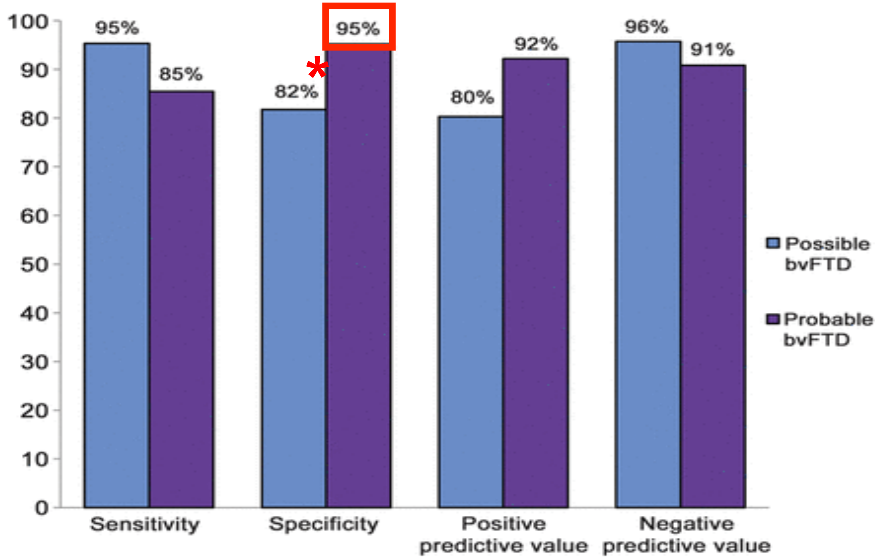


Seeley et al., Arch Neurol 2008

PPA



Gorno-Tempini et al., Ann Neurol 2010



Total sample = 156 path-proven patients with dementia

*False positive subjects were: 9 AD, 1 mixed AD + LBD, 1 LBD, 1 prion disease, 2 cerebrovascular disease, 1 not-specific changes

Harris et al., Neurology 2013

MRI IN DEMENTIA

Brain atrophy in non-AD dementia

DLB revised diagnostic criteria

Supportive biomarkers

Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

McKeith et al., Neurology 2017

If hippocampal atrophy!

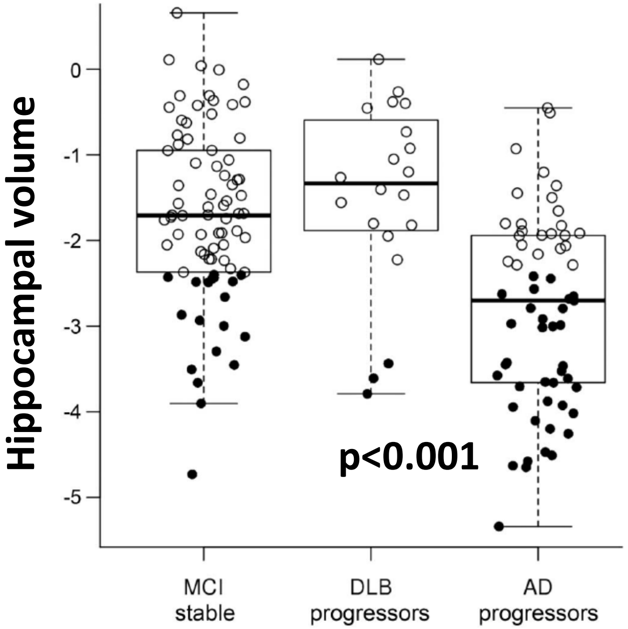
AD pathology

More rapid clinical course

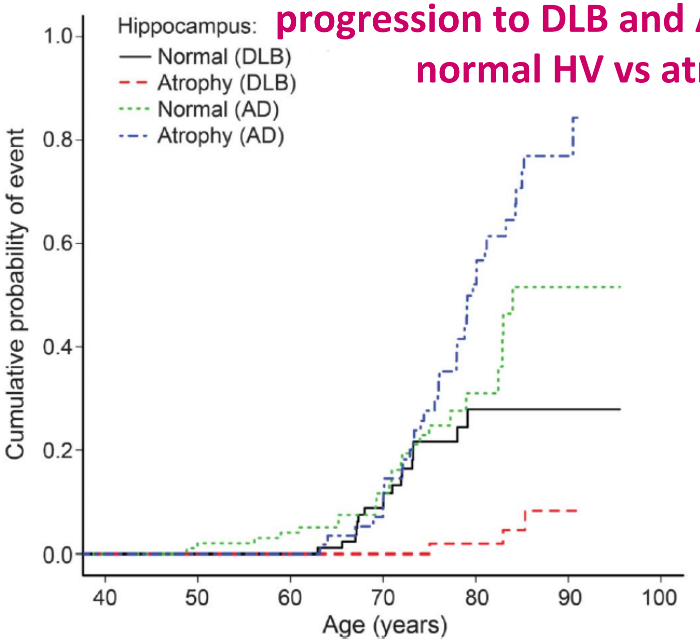
Cognitive decline

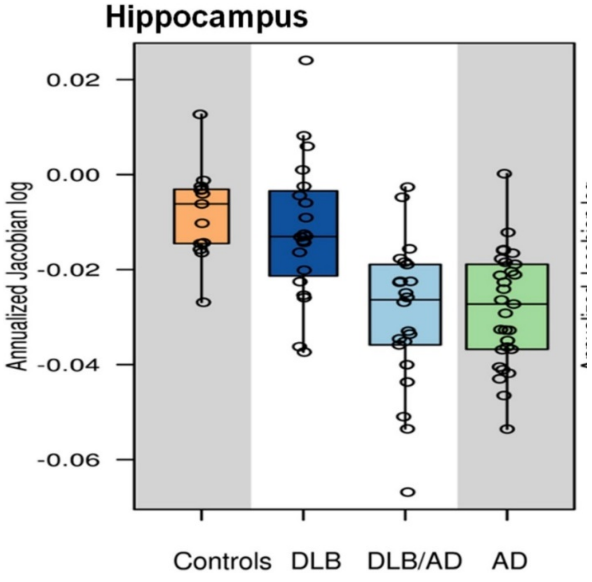
Progression of motor symptoms

AD *vs* DLB risk (2 years)



Cumulative incidences of progression to DLB and AD by normal HV vs atrophy



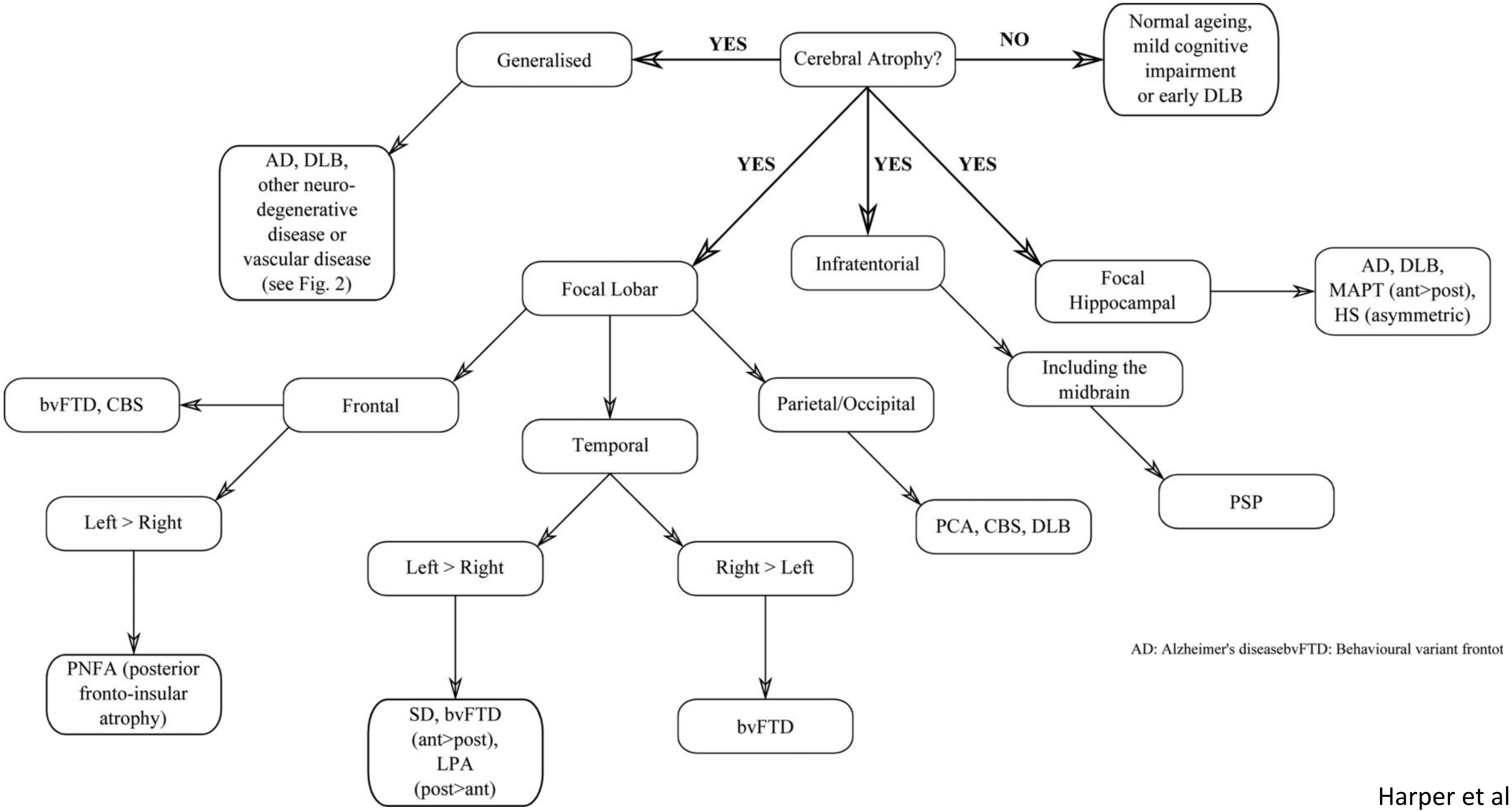


Nedelska et al., Neurobiol Aging 2015

MRI IN DEMENTIA

Brain atrophy in diagnosis

An algorithmic approach to (GOOD) structural imaging in dementia



Harper et al., JNNP 2014

MRI IN DEMENTIA

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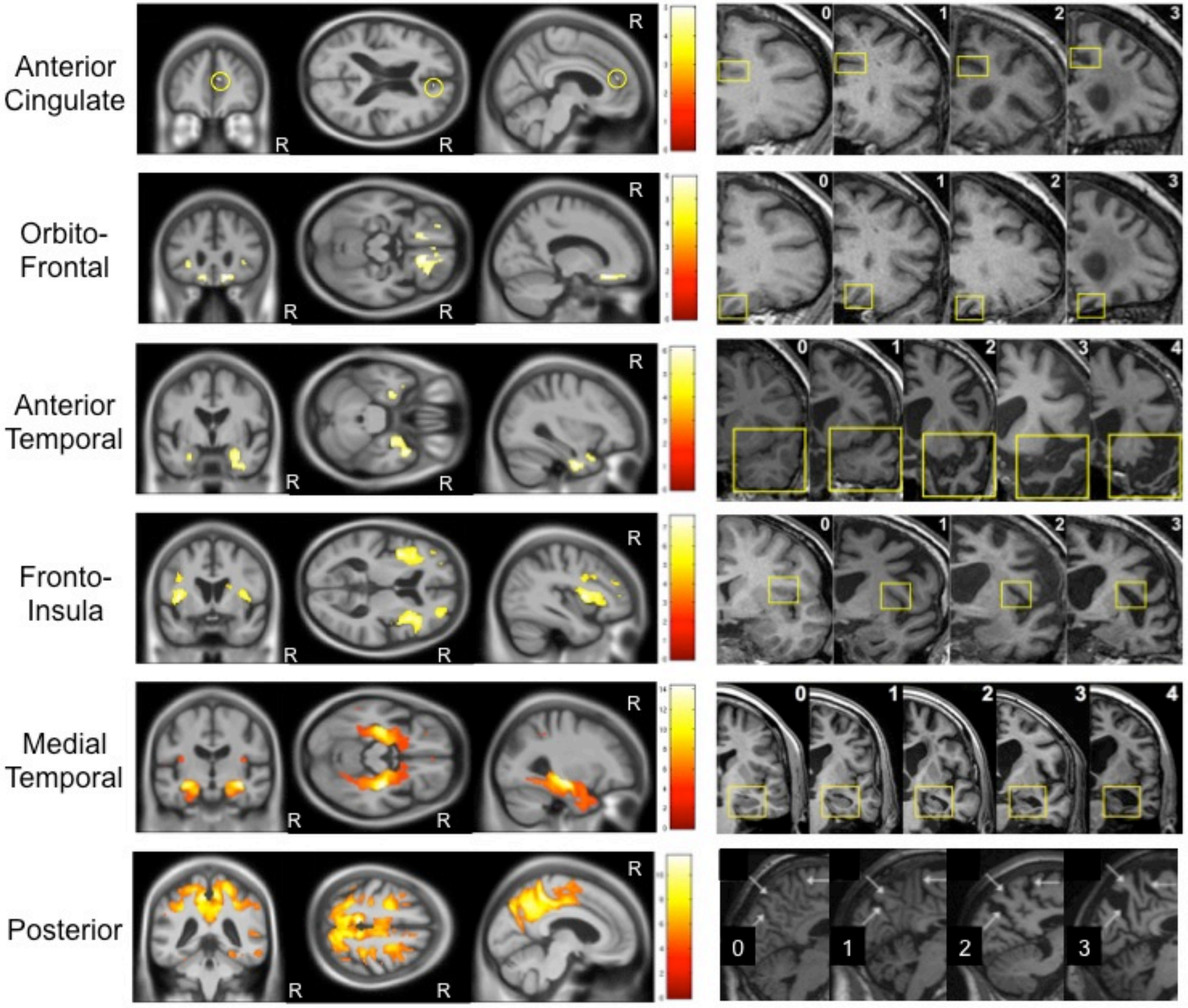
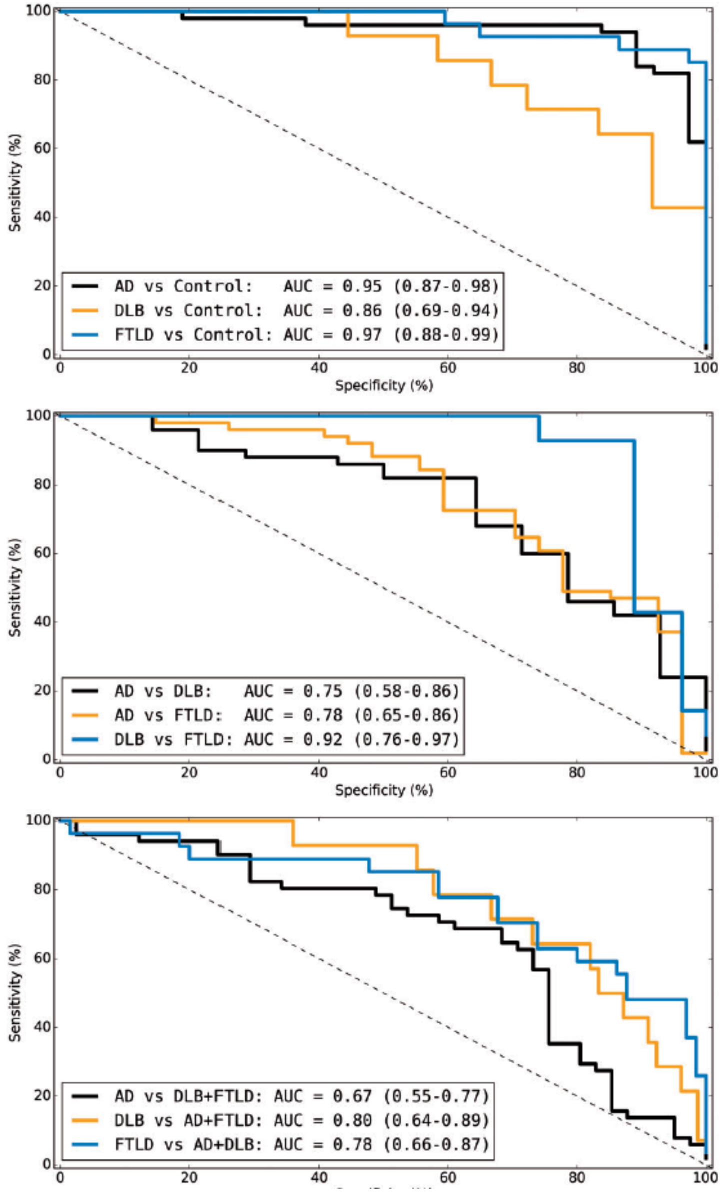
MRI IN DEMENTIA

Visual ratings *vs* quantitative measures

VBM *vs* 6 visual rating scales in 184 path-proven cases



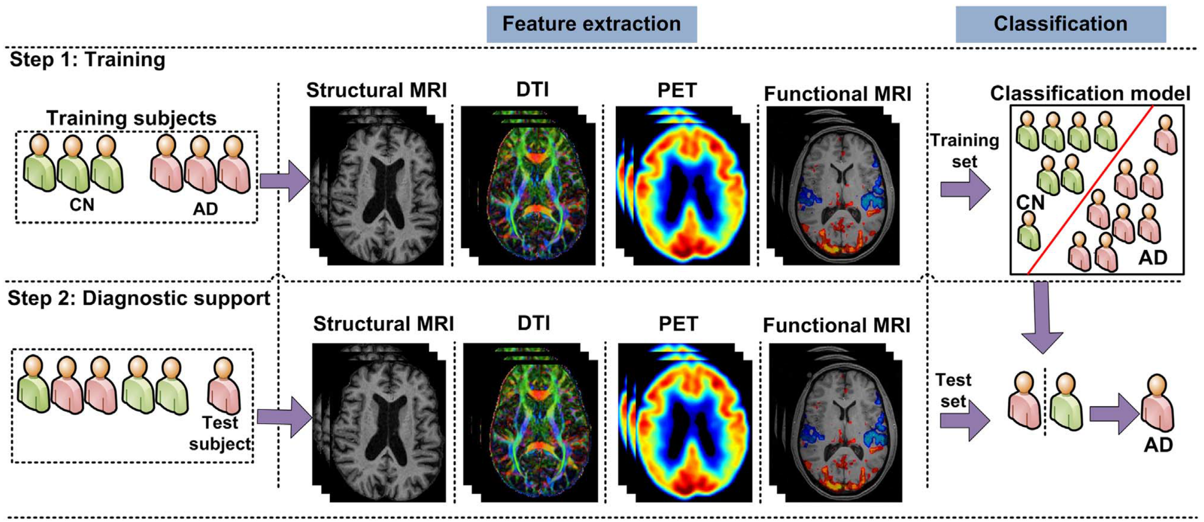


Harper et al., Brain 2016

< 3 minutes to apply all 6 scales!!

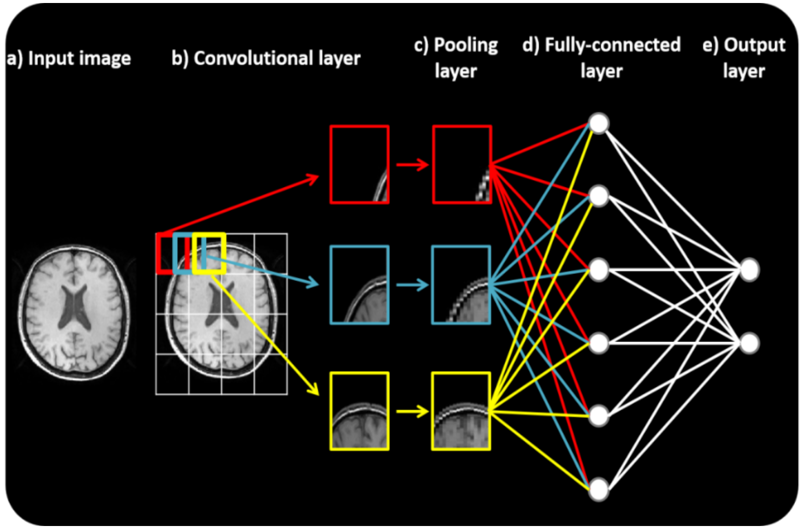
MRI IN DEMENTIA

Supervised automatic tools



Rathore et al., NeuroImage 2017

Deep learning & MRI in AD



Basaia et al., NeuroImage Clin 2018

	Subjects					Type	Classification algorithm	Database	Classification accuracy			
	AD	MCI	pMCI	sMCI	CN				AD/CN	MCI/CN	AD/MCI	sMCI/pMCI
(Fan et al., 2008b)	–	15	–	–	15	SFC	SVM	BLSA	–	90.00	–	–
(Vemuri et al., 2008)	190	–	–	–	190	SFC	SVM	ADNI	89.30	–	–	–
(Kohannim et al., 2010)	158	264	–	–	213	SFC	SVM	ADNI	93.81	75.49	–	–
(Davatzikos et al., 2011)	–	–	69	170	–	SFC	SVM	ADNI	–	–	–	61.70
(Dukart et al., 2011a)	21	–	–	–	13	SFC	SVM	Leipzig	100.00	–	–	–
(Cui et al., 2011)	96	–	56	87	111	SFC	SVM	ADNI	–	–	–	67.13
(Cui et al., 2012)	–	79	–	–	204	SFC	SVM	SMAS	–	71.09	–	–
(Dukart et al., 2013)	49	–	–	–	41	SFC	SVM	ANDI, Leipzig	90.00[a]	–	–	–
(Zhang et al., 2014)	24	57	–	–	97	SFC	Kernel SVM decision-tree	OASIS	96.00	85.00	88.00	–
(Zhu et al., 2014)	51	99	–	–	52	SFC	SVM	ADNI	95.90	82.00	–	–
(Li et al., 2014a)	21	–	–	–	15	SFC	SVM	TH	94.30	–	–	–
(Apostolova et al., 2014)	95	182	–	–	111	SFC	SVM	ADNI	85.00	79.00	70.00	–
(Moradi et al., 2015)	200	–	164	100	231	SFC	LDS, Random forest	ADNI	–	–	–	81.72
(Zheng et al., 2015)	163	–	104	94	189	SFC	SVM	ADNI	92.11	–	–	79.37
(Tang et al., 2016)	29	–	–	–	23	SFC	LDA, SVM	TH	94.60	–	–	–
(Schouten et al., 2016)	77	–	–	–	173	SFC	Elastic net classifier	PRODEM	93.00	–	–	–

MCI converters *vs* MCI stable

Data source: ADNI + HSR
Image sample size:
(228+25) MCI converters
(459+21) MCI stable
(training, validation)

Transfer learning AD vs HC

Data augmentation

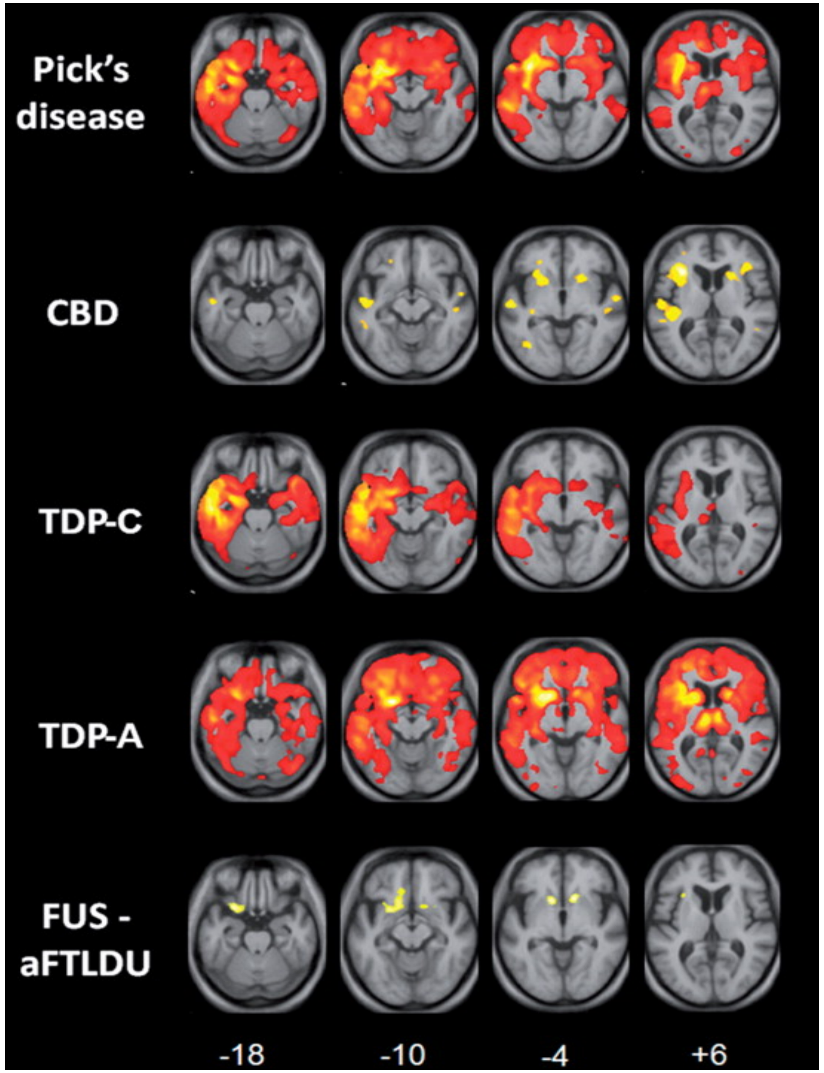
Image sample size:
(500+500) MCI converters
(500+500) MCI stable

Classifier: MCI converters *vs* MCI stable
Accuracy: 74.9 %
Sensitivity: 75.8 %
Specificity: 74.1 %

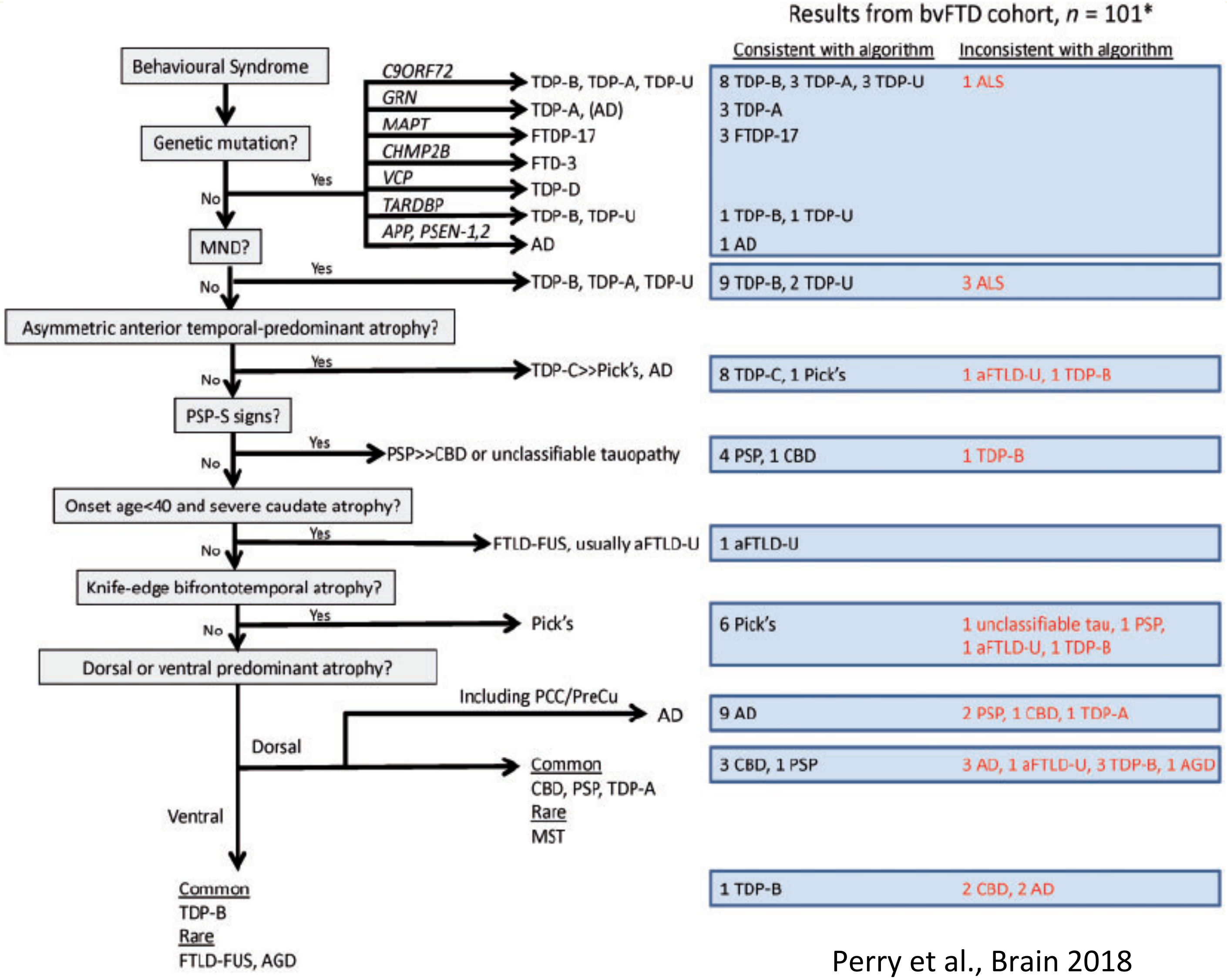
MRI IN DEMENTIA

Specificity to pathology

FTD spectrum



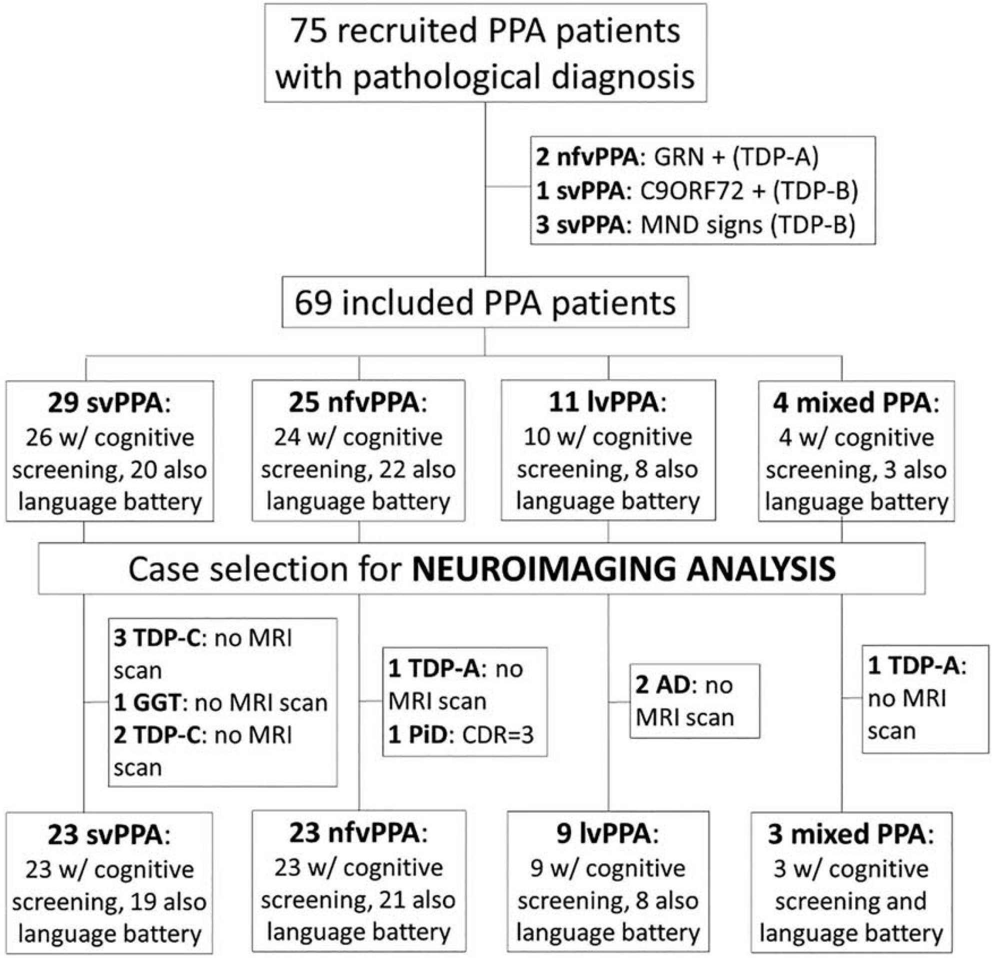
Rohrer et al., Brain 2011



Perry et al., Brain 2018

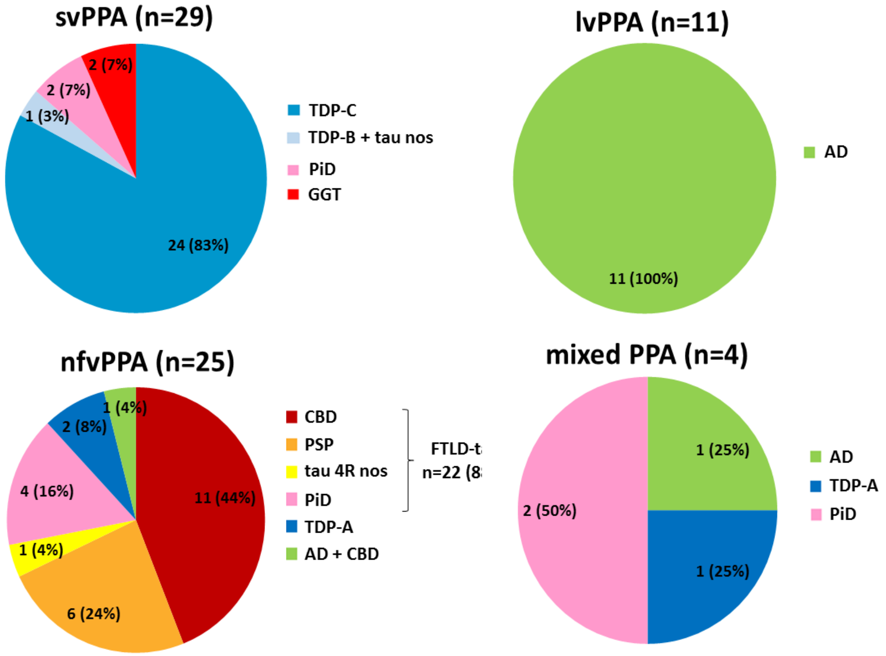
MRI IN DEMENTIA

Specificity to pathology

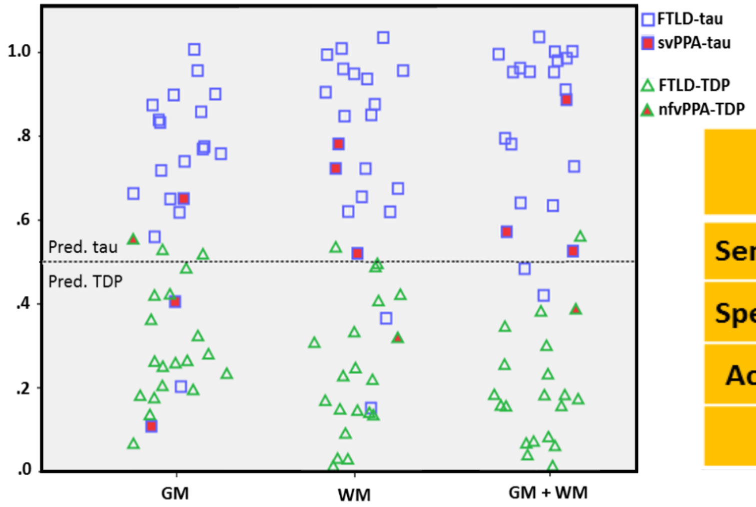


Spinelli et al., Ann Neurol 2017

Clinical + review of conventional neuroimaging (MRI, CT and/or PET)



FTLD TAU *vs* FTLD TDP-43



	GM	WM	GM + WM
Sensitivity (%)	85.7	90.5	90.5
Specificity (%)	95.0	90.0	95.0
Accuracy (%)	90.2	90.2	92.7
AUC (%)	91.0	93.0	96.4

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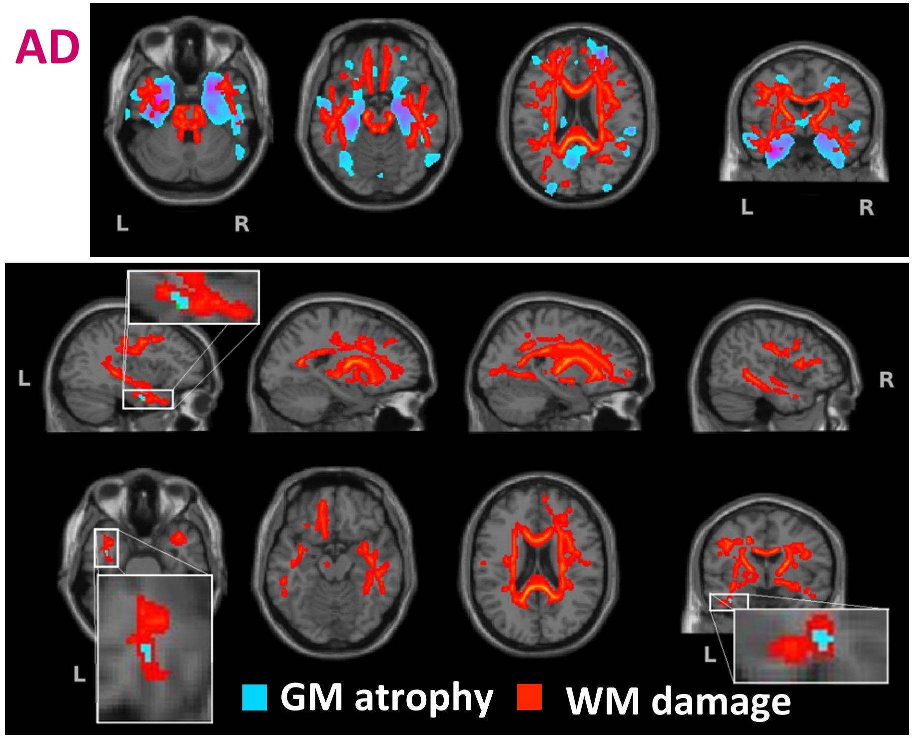
MRI IN DEMENTIA

The contribution of advanced MRI

AD

MCI

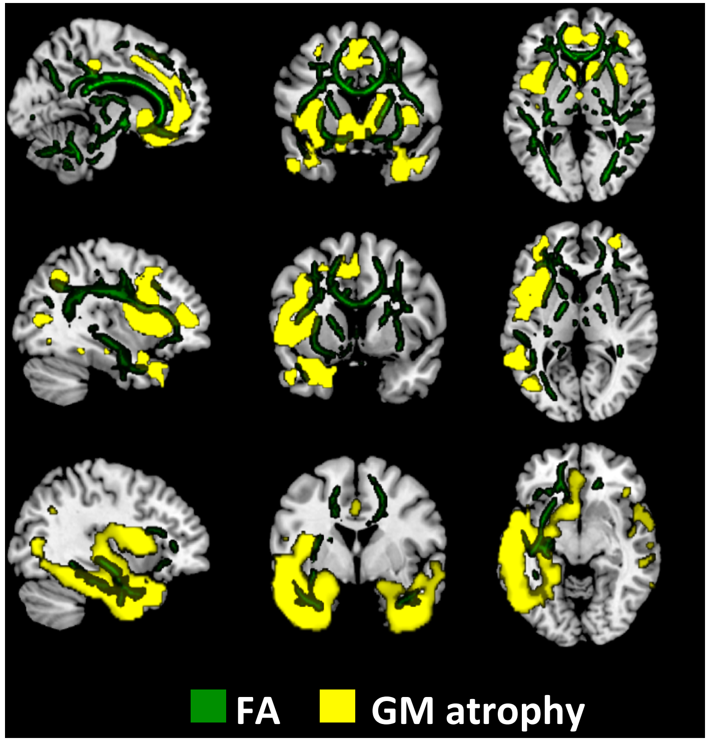


Agosta et al., Radiology 2011

bvFTD

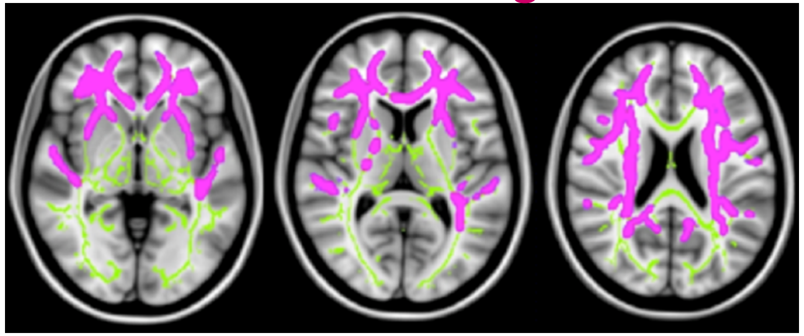
Nonfluent

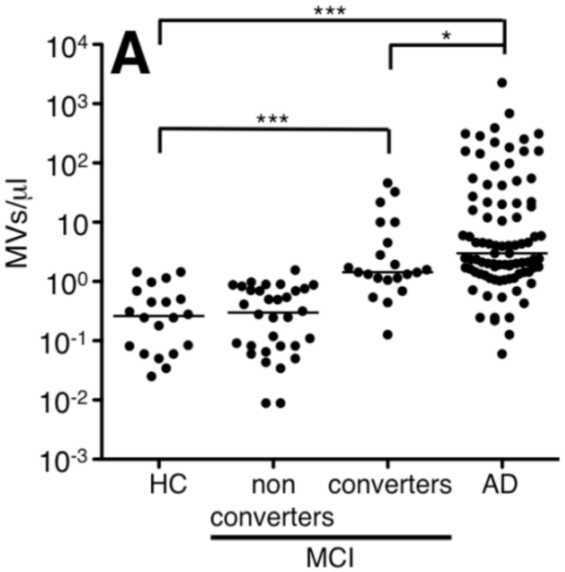
Semantic



Agosta et al., Cereb Cortex 2012

MVs *vs* WM damage in MCI





Increased CSF MVs in AD and MCI

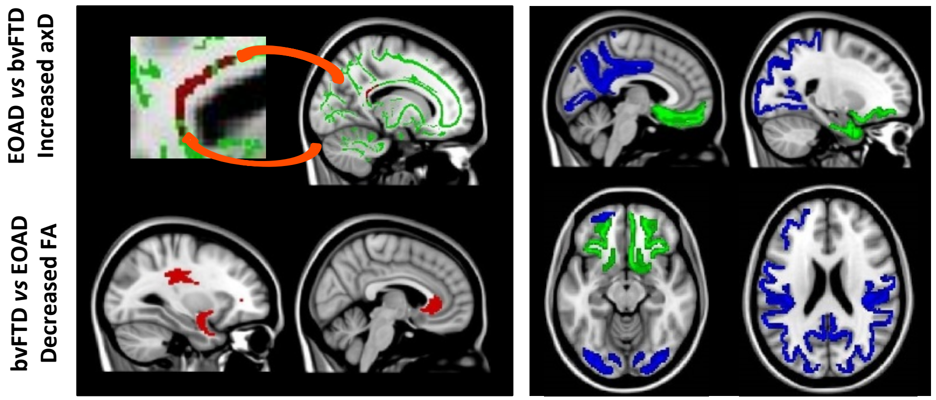
Agosta et al., Ann Neurol 2014

MRI IN DEMENTIA

The contribution of advanced MRI

bvFTD *vs* EOAD

WM damage | **GM atrophy**



EOAD ■ bvFTD ■

Random forest analysis: bvFTD *vs* EOAD

White matter	NVI	Gray matter	NVI
R uncinate axD	100.0	L Inferior parietal th.	100.0
R uncinate radD	98.3	R Temporal pole th.	96.1
R uncinate MD	80.5	L cingulate th.	75.8

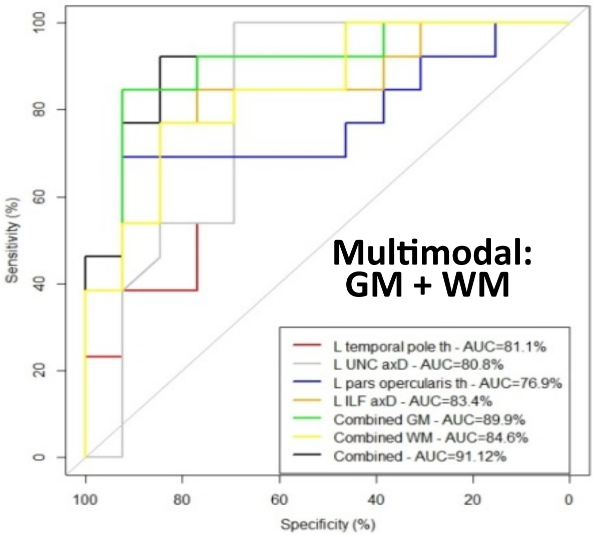
Canu et al., Neuroimage Clin 2017

bvFTD *vs* PPA

bvFTD *vs* nonfluent	L SLF radD	0.74%
	Anterior CC radD	0.74%
bvFTD *vs* semantic	L ILF axD	0.91%
	L uncinate axD	0.88%
Nonfluent *vs* semantic	L uncinate axD	0.96%
	L ILF axD	0.98%

Agosta et al., Cereb Cortex 2012

Semantic *vs* nonfluent PPA

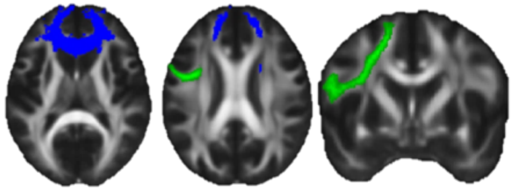


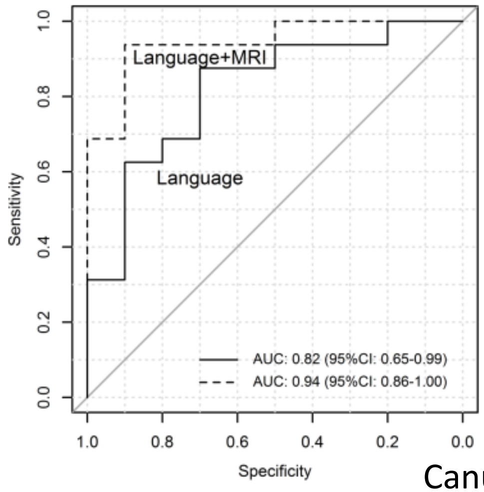
Agosta et al., Radiology 2015

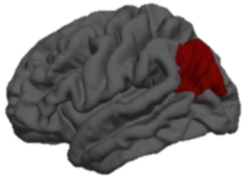
Logopenic *vs* nonfluent PPA

Language:
Confrontation naming
Object knowledge
Single word comprehension
Syntactic comprehension
Repetition
Apraxia of speech

+



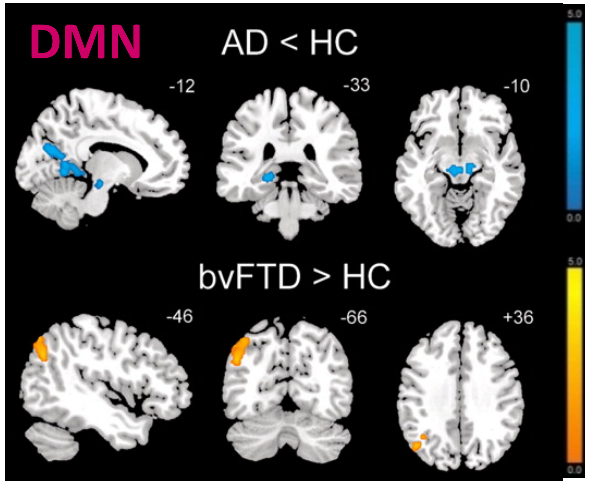


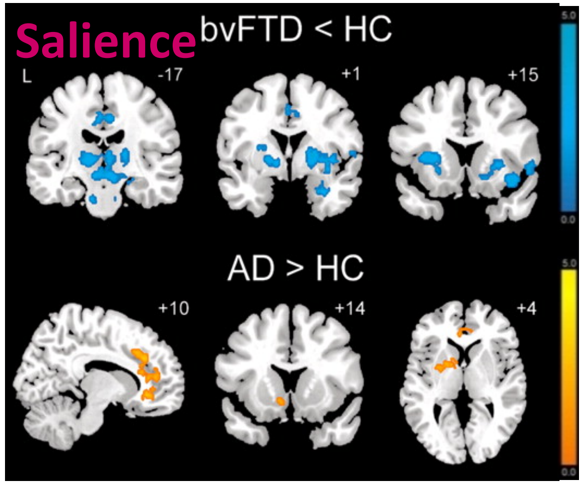


Canu et al., Cortex 2018

MRI IN DEMENTIA

The contribution of advanced MRI

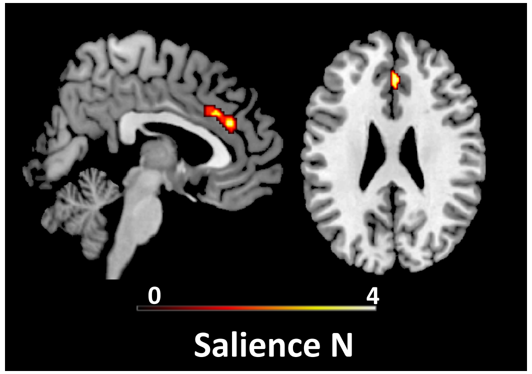




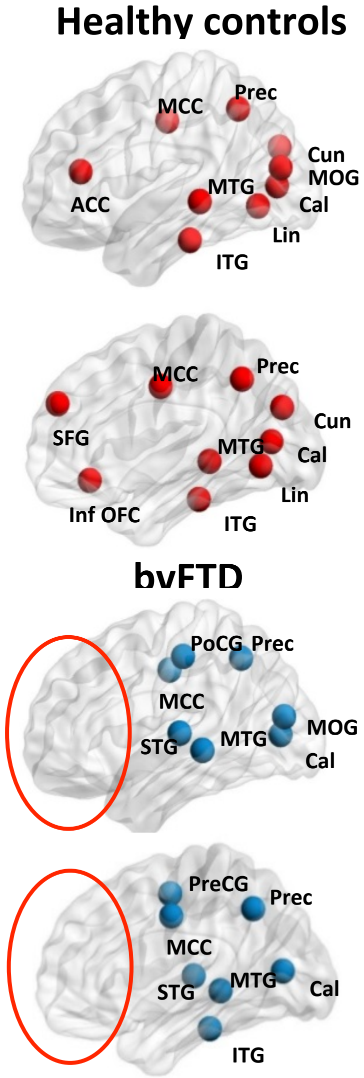
Salience N - DMN score: sensitivity 92% specificity 96%

Zhou et al., Brain 2010

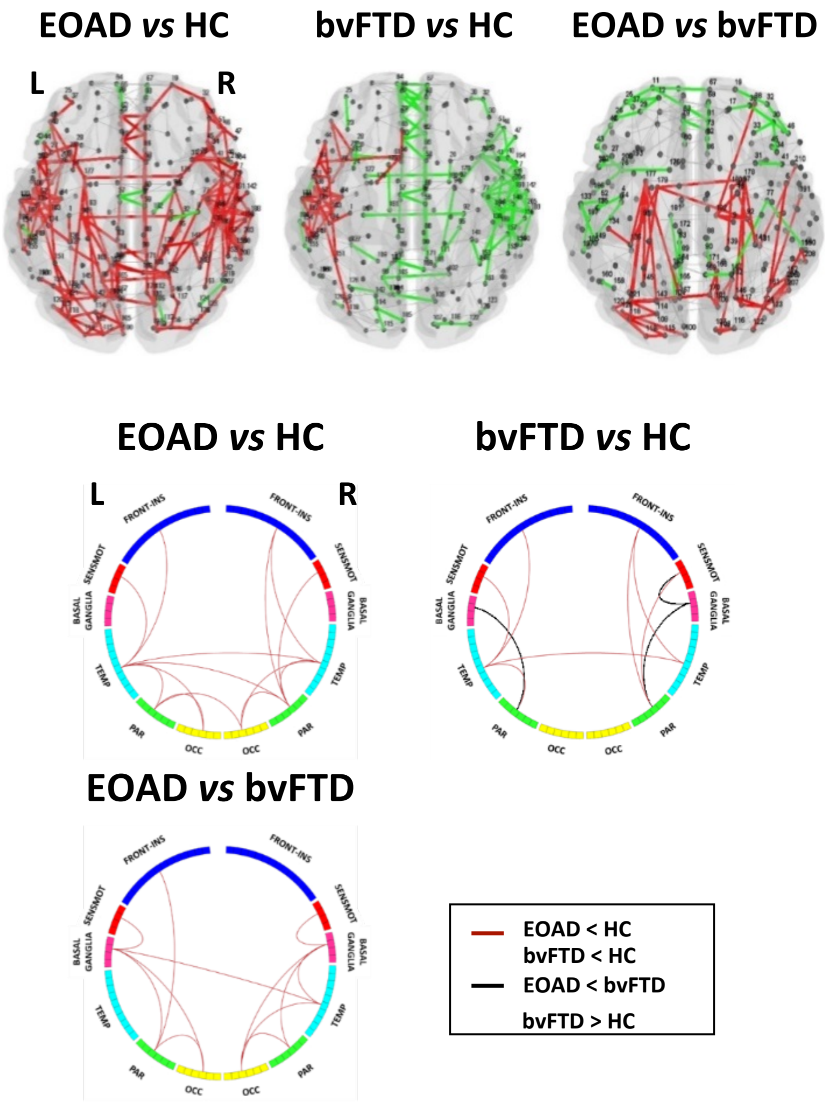
bvFTD *vs* AD



Filippi et al., Cortex 2013



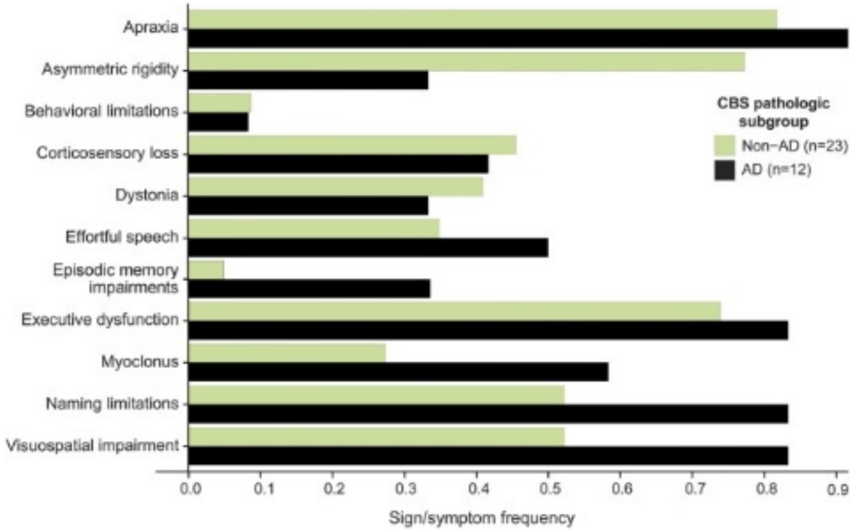
Agosta et al., Neurology 2013



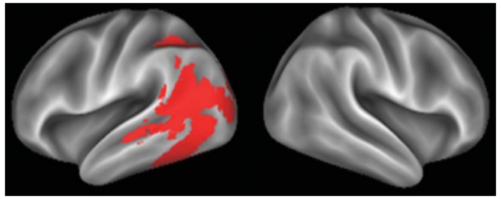
Filippi et al., Neurology 2017

MRI IN DEMENTIA

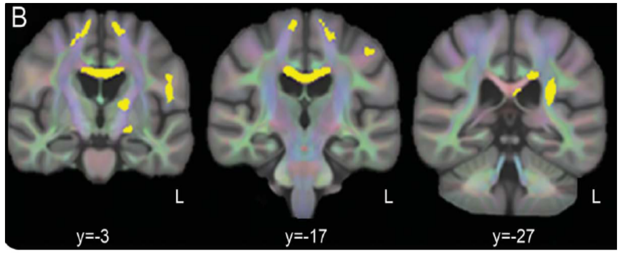
The contribution of advanced MRI



CBS-AD > CBS-noAD

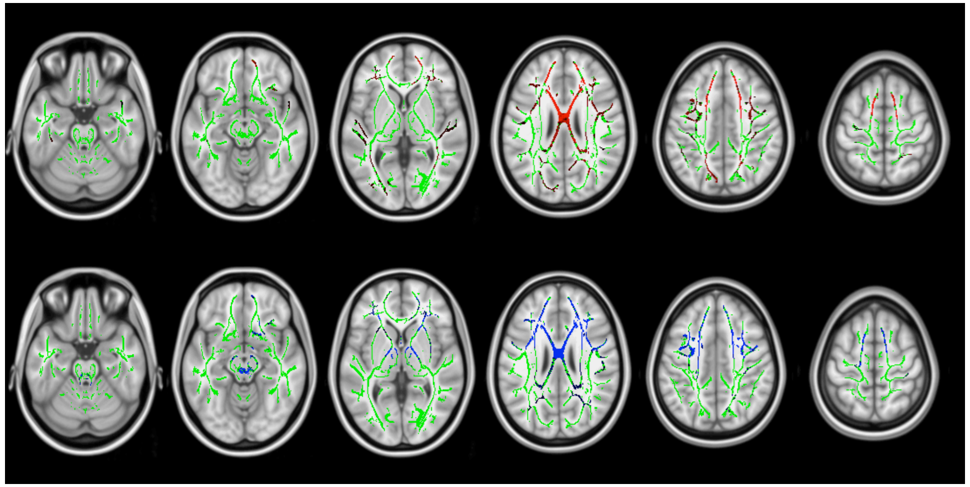


CBS-noAD > CBS-AD

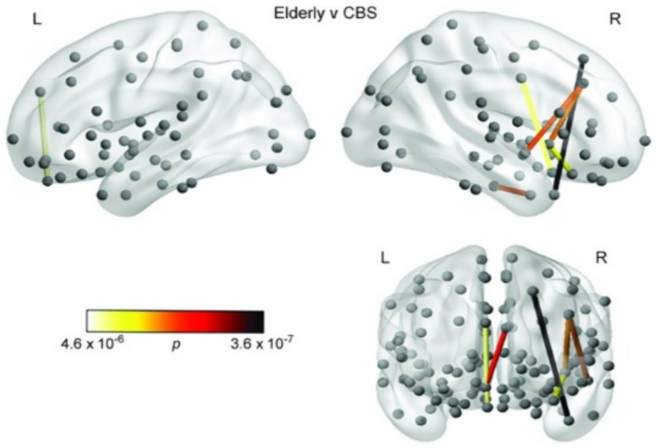


McMillan et al., Neurology 2016

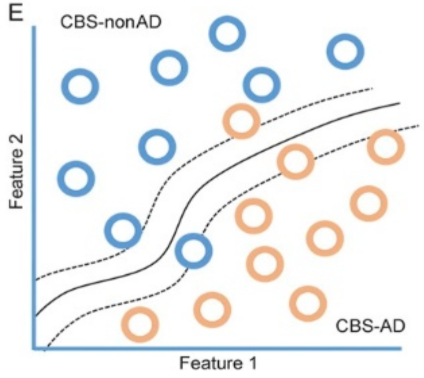
FTLD TAU *vs* TDP-43

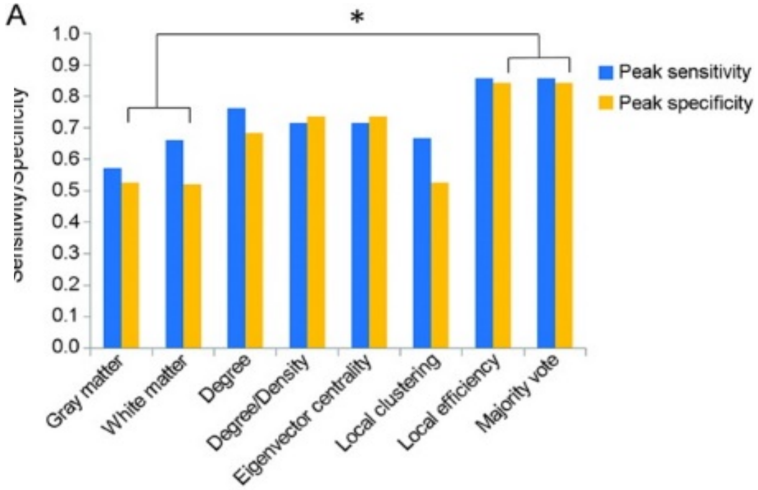


Agosta et al., Human Brain Mapp 2015

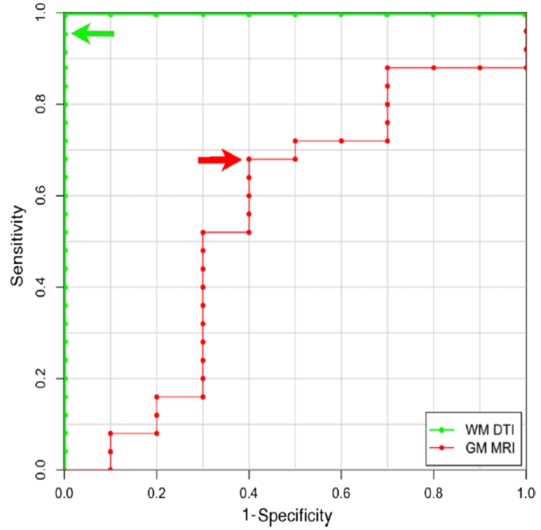


Medaglia et al., Neurology 2017





FTLD TAU *vs* TDP-43



McMillan et al., JNNP 2013

MRI CONTRIBUTION

Conclusions

- **Structural MRI is mandatory to exclude the presence of secondary causes**
- **Structural MRI provides the topography of atrophy which might inform on the underlying neurodegenerative etiology**
  - ✓ **MRI is more than hippocampal volume**
  - ✓ **Visual ratings *vs* quantitative measures? Supervised tools may be the answer**
  - ✓ **Select patients for further "pathophysiological" markers**
  - ✓ **Strong utility in non-AD dementia**
  - ✓ **(Possibility to enrich for presence/absence of atrophy)**
  - ✓ **(Stage the disease)**
- **Future role for MRI may include measuring white matter and resting state fMRI changes**

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