6-7-8 NOVEMBRE 2017
San Benedetto del Tronto (AP)

Imaging radiologico e malattie degenerative cerebrali

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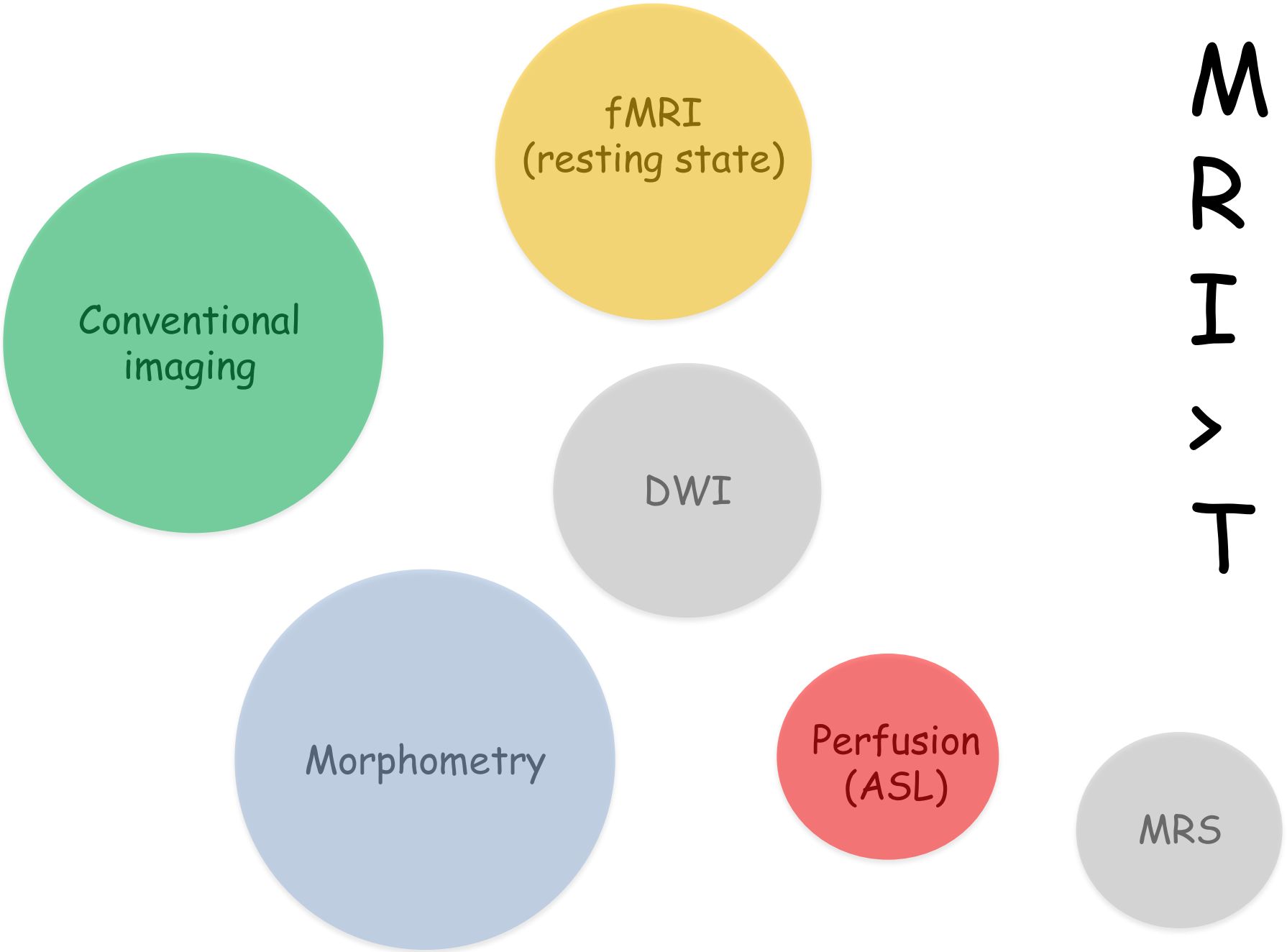
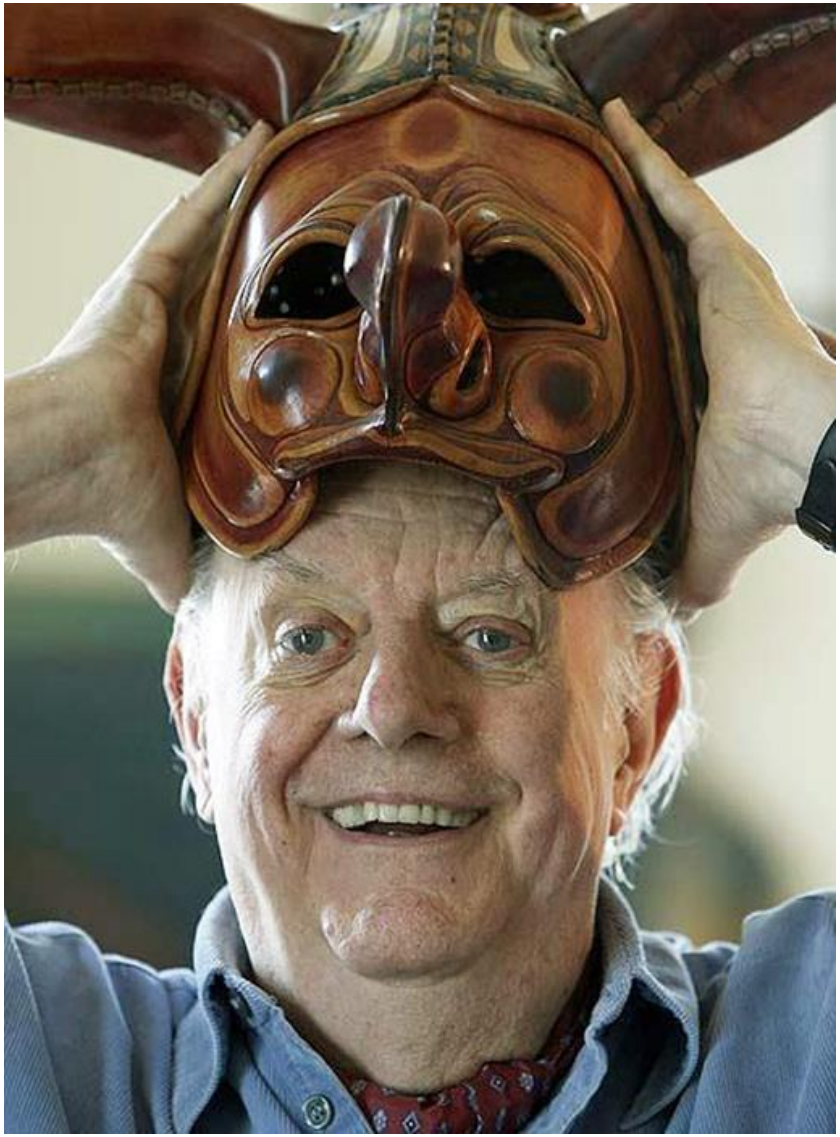
Outline

- (Successful) Ageing Changes
- Alzheimer's Disease
- Frontotemporal Degeneration
- Primary Progressive Aphasia Phenotypes
- Parkinson and parkinsonisms
- Motor neuron diseases

- Initial stages of neurodegenerative disease may be undistinguishable from normal ageing
- Neuroradiological findings of neurodegenerative disease are rarely specific, expecially at early stage of disease
- No NRX without a clinical indication


fMRI
(resting state)
Conventional
imaging
DWI
Morphometry
Perfusion
(ASL)
MRS
MRI > T

Successful Ageing!



"90 anni una folle età e mi indigno ancora"

Structural MRI in (Successful) Ageing

- ✓ Normal Thinning of the Cerebral Cortex
- ✓ Virchow-Robin Spaces
- ✓ Periventricular Caps and Leukoencephalopaty
- ✓ Iron Deposition

(Successful) Ageing

Brain Volume Loss:

✓Annualized rate of global BV loss in normal individuals ~ 0.18% / yr (< 40 y/o)

✓Starts as early as post-teenage

✓Depends on brain region

- (Frontal++)

✓Accelerates with age: ~ 0.35% /yr (> 40 y/o), ~ 0.5% / yr (Elderly)

Raz et Al, Neubiorev 2006 Sluimer et Al, Radiology 2008

Cortical Thinning:

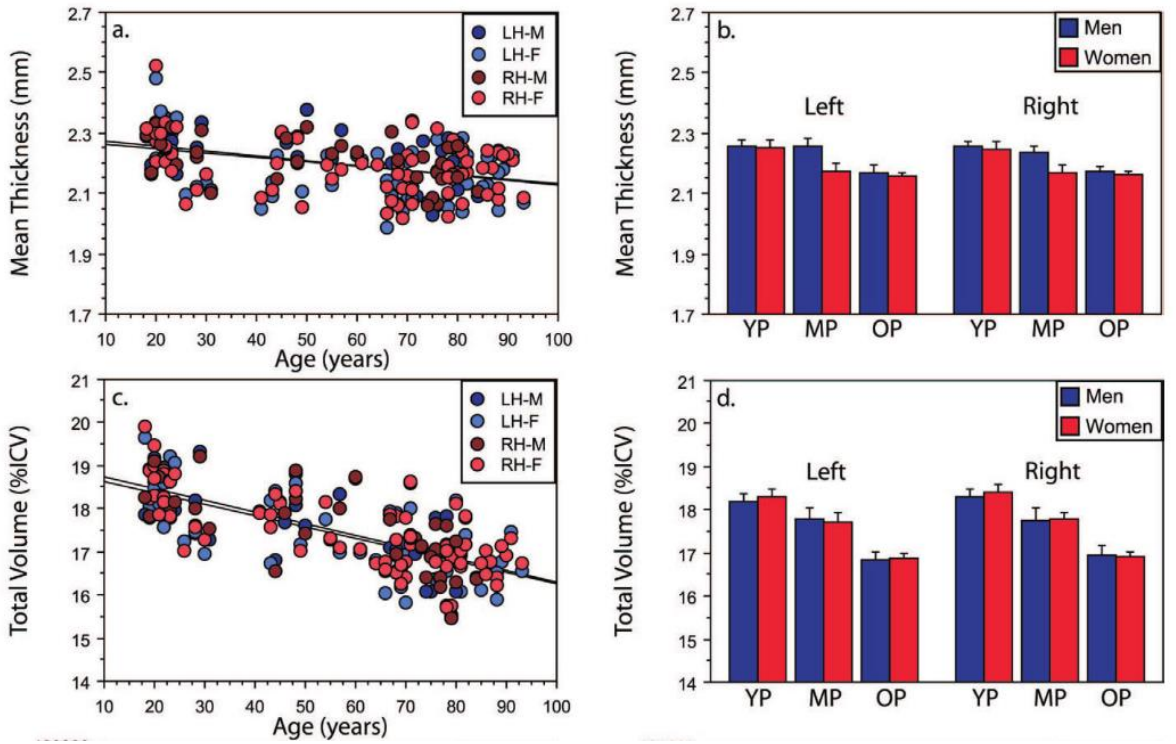
✓Neuron Loss

✓Dendritic Arborization reduction

✓Neuron Shrinkage

Salat et Al, Cereb Cortex 2004

(Successful) Ageing



Thinning of the Cerebral Cortex in Aging

Cerebral Cortex V 14 N 7 © Oxford University Press 2004; all rights reserved

Salat, Cereb Cortex 2004

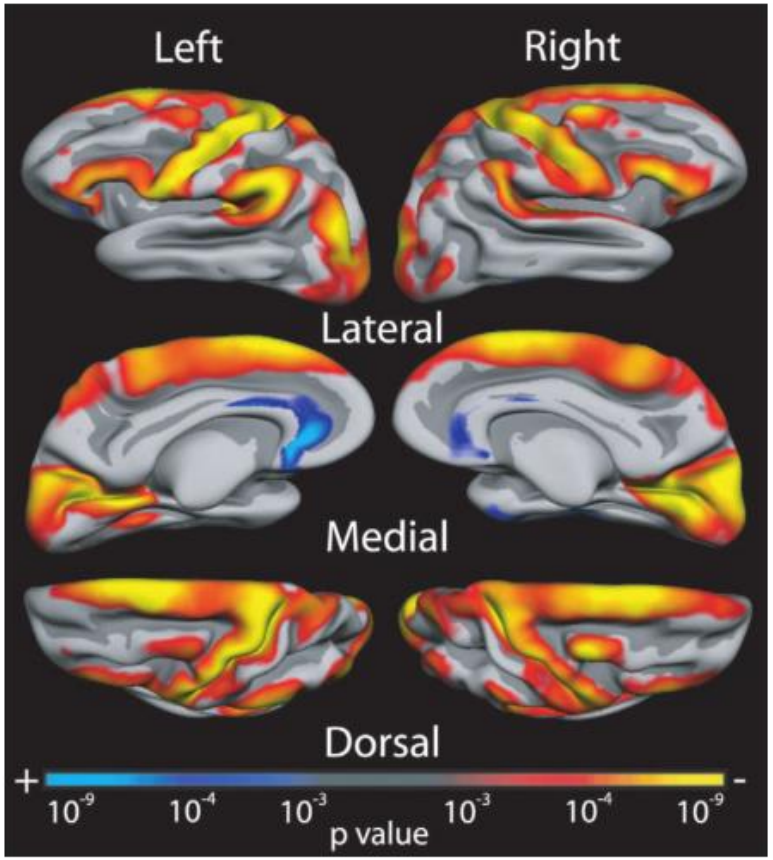


Figure 3. Age-associated map of cortical thinning. Surface maps of cortical thinning in aging were generated by assessing the influence of age on thickness (using the general linear model) at each vertex across the entire cortical mantle. Maps are presented on the semi-inflated cortical surface of an average brain with dark gray regions representing sulci and light gray regions representing gyri. Non-neocortical regions and regions that are not part of the cortical mantle (such as the corpus callosum and thalamus) have been excluded from the analysis. The colorscale at the bottom represents the significance of the thickness change with yellow indicating regions of most significant thinning.

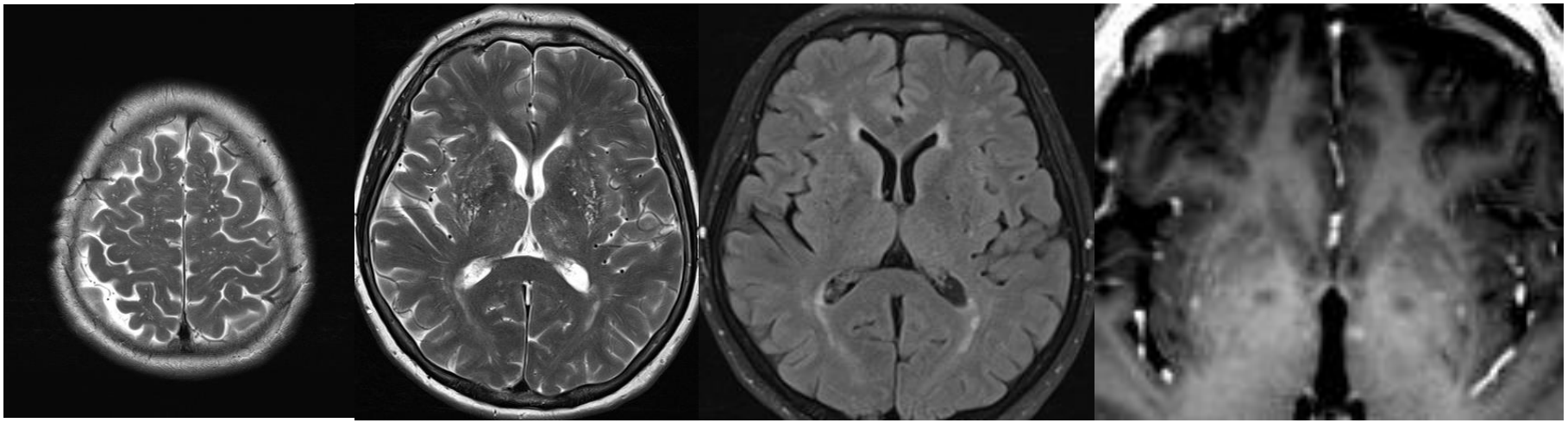
Spatial distribution:
frontal ++

(Successful) Ageing

- Enlarged Virchow-Robin spaces: Perivascular extension of subarachnoid space

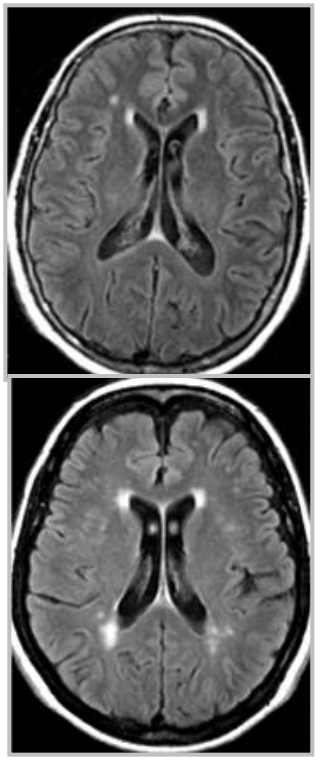
•Normally found in early adulthood in the basal ganglia / mesencephalon

•Normally found in elderly at the vertex / deep white matter



M, 51y/o

(Successful) Ageing

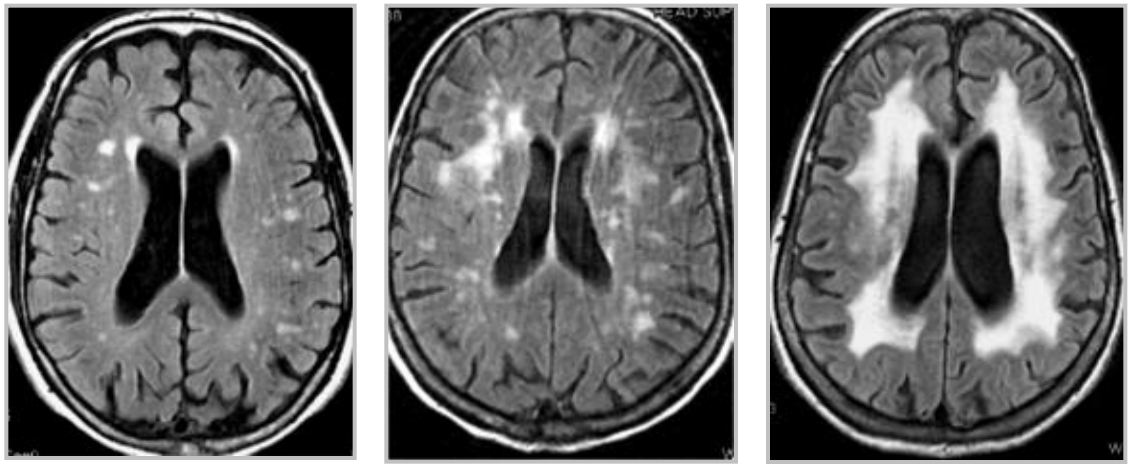


Periventricular caps (T2 Hyperintensity):

✓Ependymal loss, subependymal gliosis and widened extracellular space
✓Starts > 40-50 years of age
✓Difficult to distinguish from chronic ischemia/leukoencephalopathy

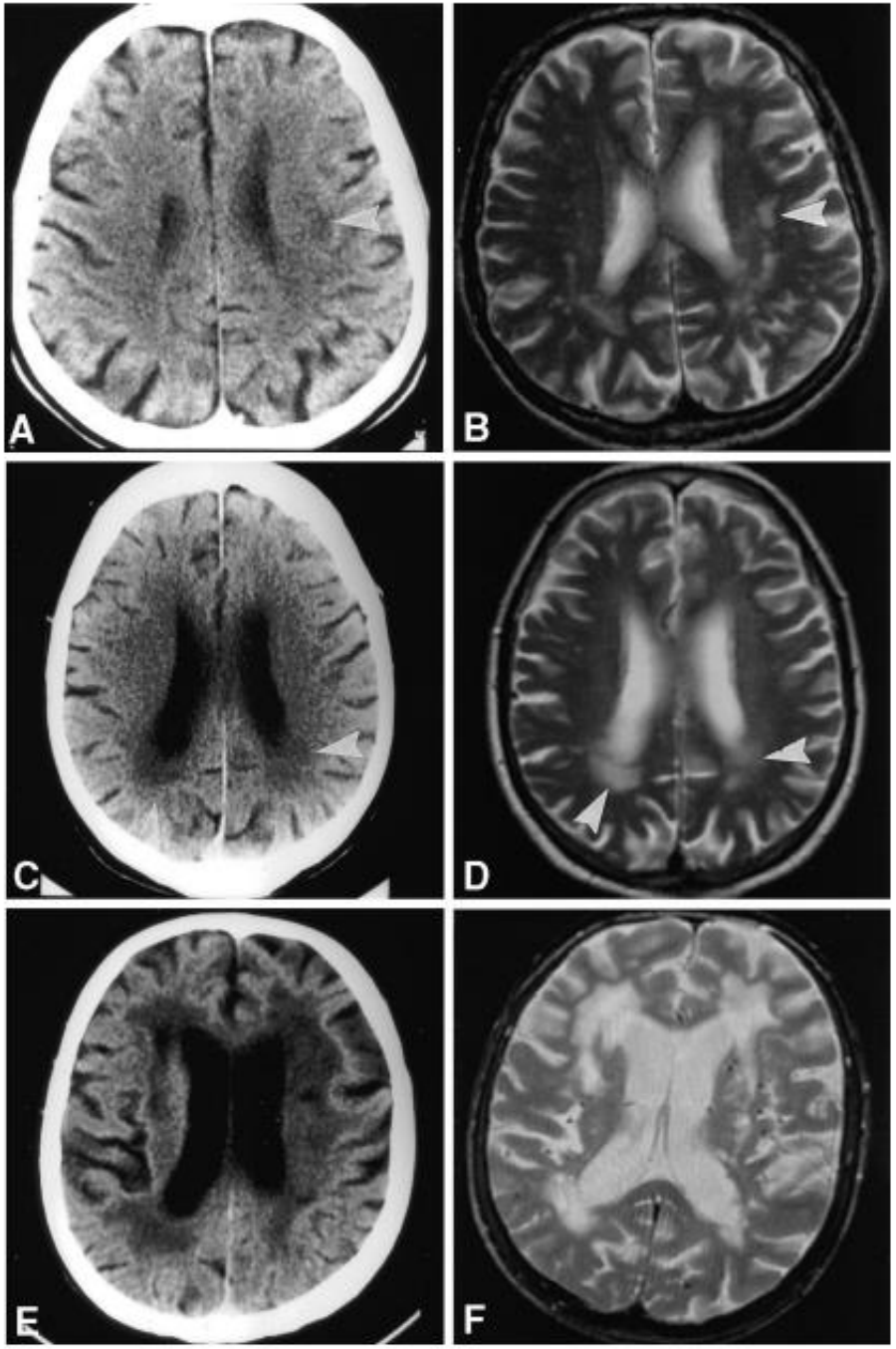
White Matter Lesions (T2 Hyperintensities):

✓ Chronic / Incomplete infarction
✓ Tissue rarefaction
✓ Expanded extracellular space
✓ ***Wahlund-Fazekas Classification 1: sporadic (normal); 2 initial bridging; 3 confluent (2-3 associated to cognitive impairment)***



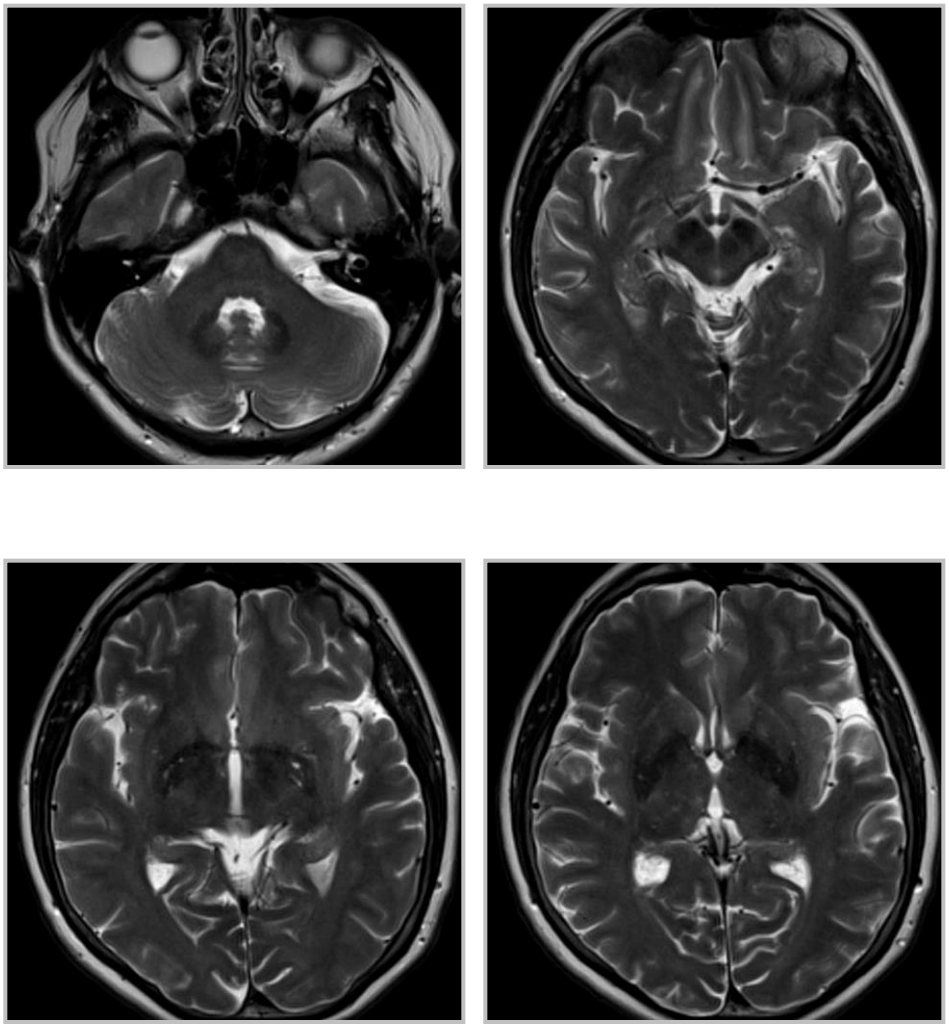
A New Rating Scale for Age-Related White Matter Changes Applicable to MRI and CT

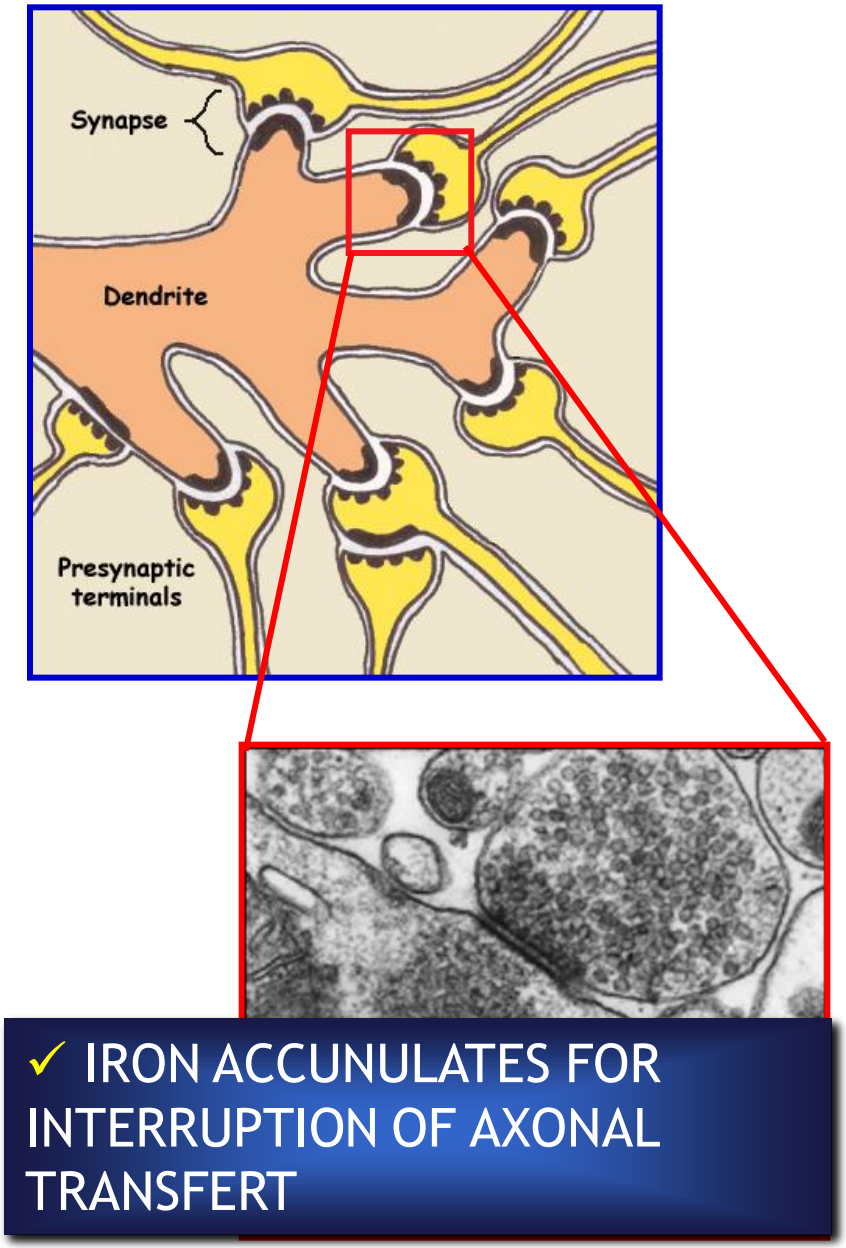
L.O. Wahlund, MD, PhD; F. Barkhof, MD, PhD; F. Fazekas, MD; L. Bronge, MD; M. Augustin, MD; M. Sjögren, MD, PhD; A. Wallin, MD, PhD; H. Ader, PhD; D. Leys, MD, PhD; L. Pantoni, MD, PhD; F. Pasquier, MD, PhD; T. Erkinjuntti, MD, PhD; P. Scheltens, MD, PhD; on behalf of the European Task Force on Age-Related White Matter Changes



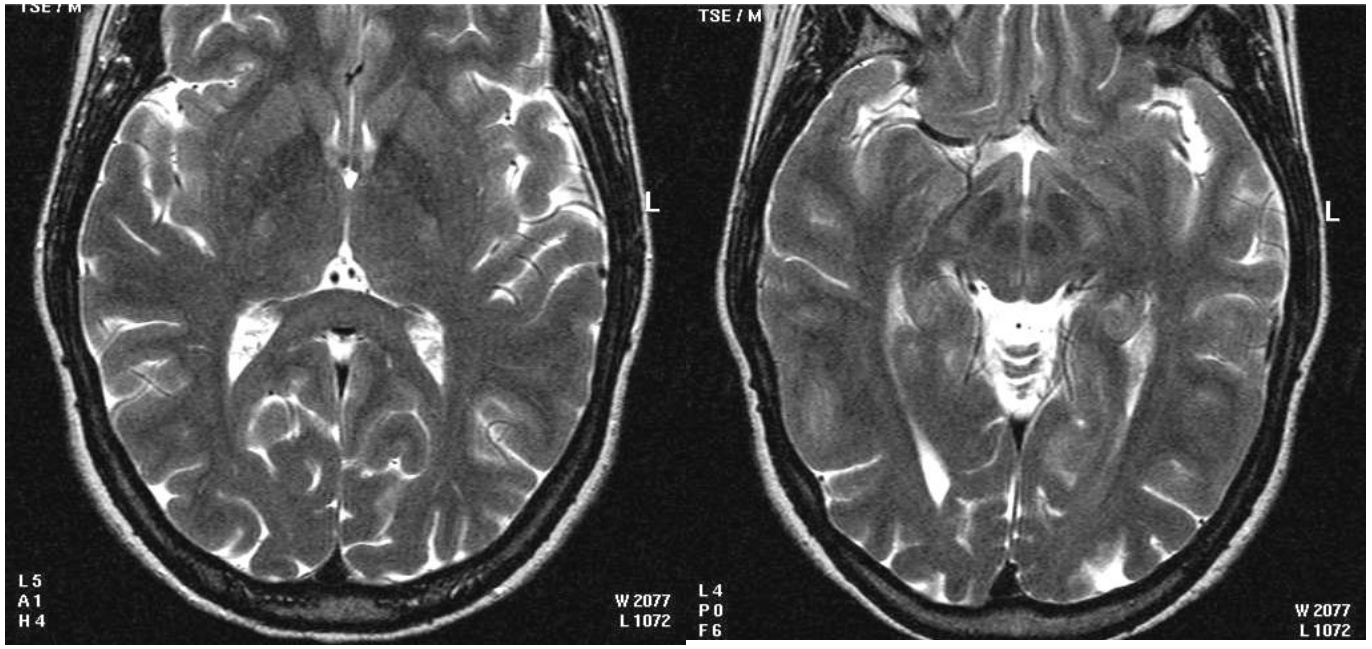
IRON DEPOSITION

✓ IRON DEPOSITION IN THE BG



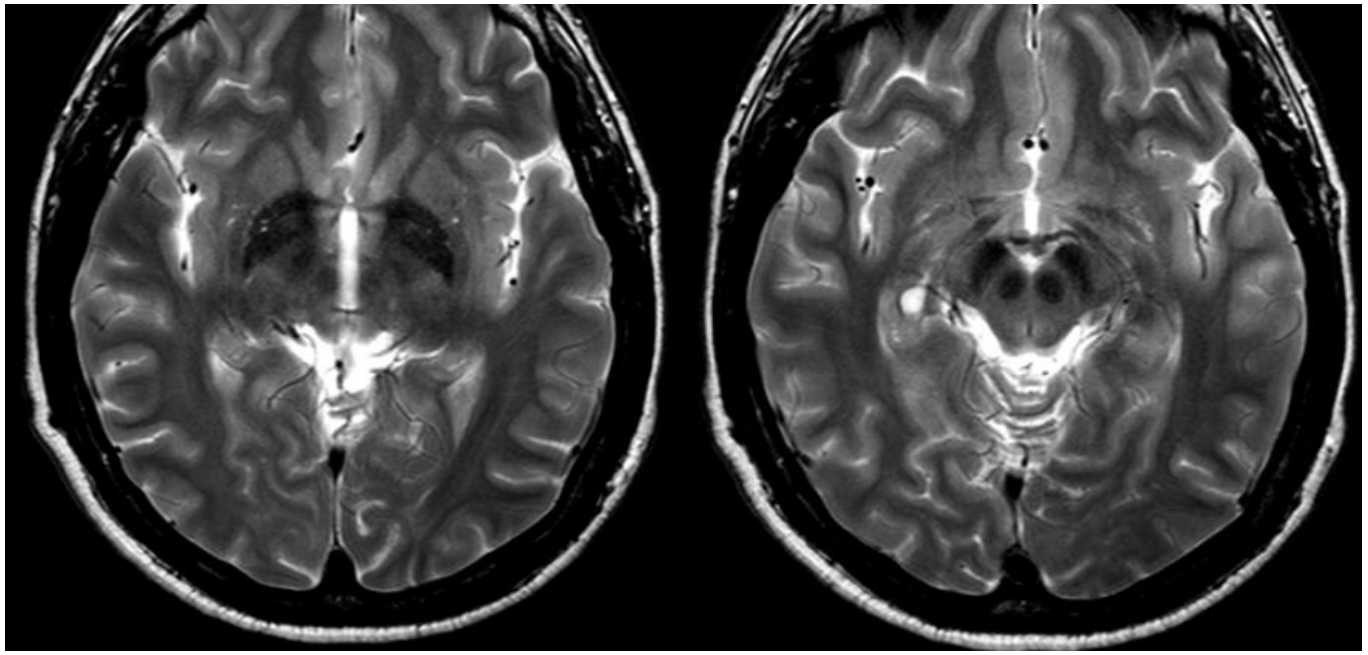


✓ IRON ACCUNULATES FOR INTERRUPTION OF AXONAL TRANSFERT



T2-w

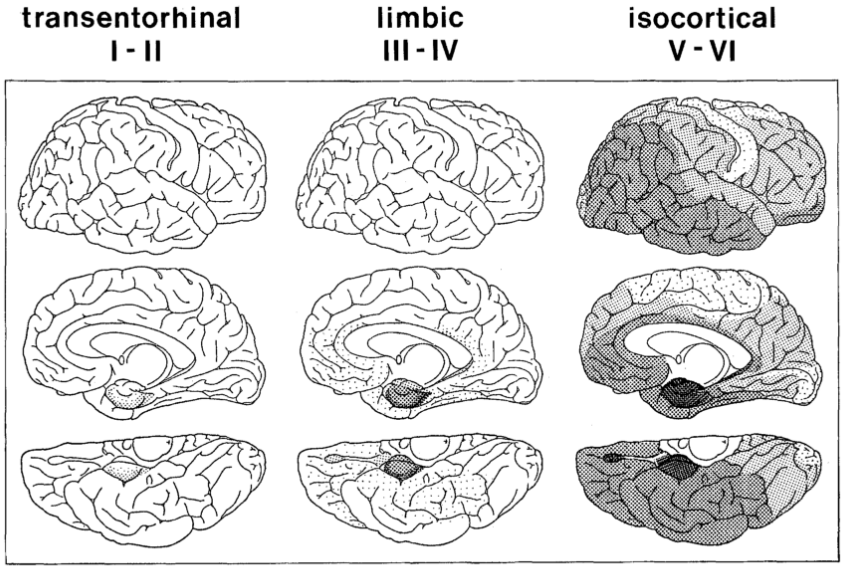
(1,5 T)



T2-w

(3 T)

MCI and Alzheimer's Disesase Neurostructural Correlates (NEUROPATHOLOGY)



Neurofibrillary changes

Neuropathological stageing of Alzheimer-related changes

H. Braak and E. Braak*

Zentrum der Morphologie, Theodor-Stern-Kai 7, W-6000 Frankfurt/Main 70, Federal Republic of Germany

Received March 6, 1991/Revised May 17, 1991/Accepted June 3, 1991

Neurofibrillary Tangles Formation in Senile AD

Braak & Braak Stages:

I-II: Enthorinal Cortex
III-IV: Limbic
V-VI: Neocortex

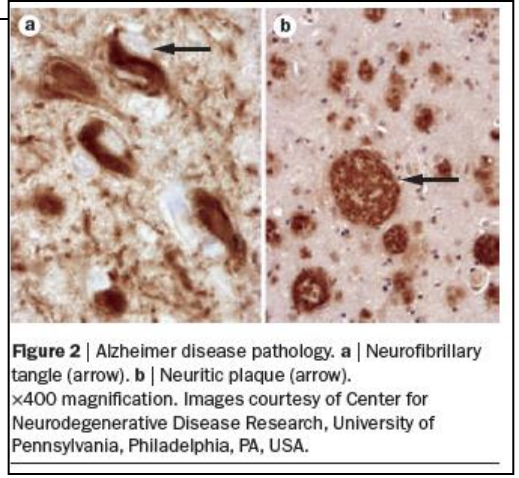
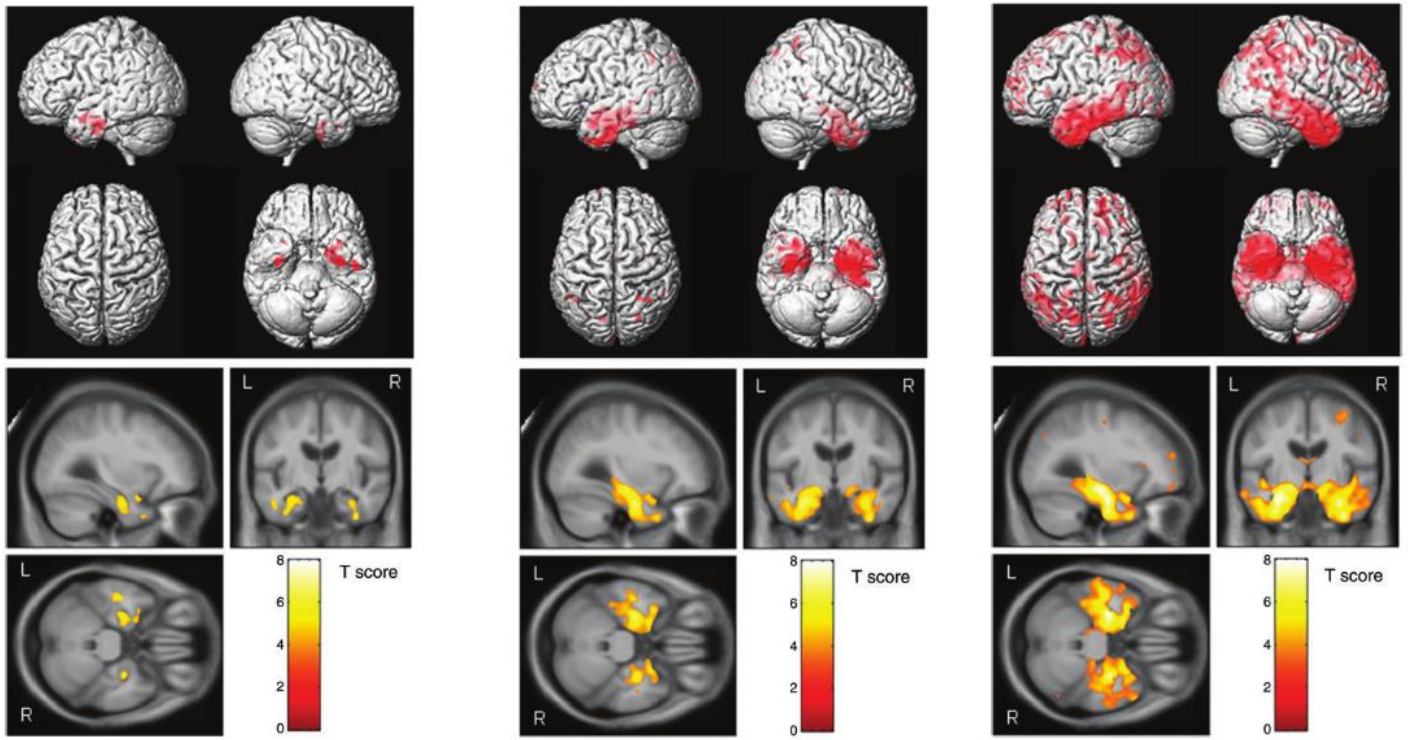


Figure 2 | Alzheimer disease pathology. **a** | Neurofibrillary tangle (arrow). **b** | Neuritic plaque (arrow). ×400 magnification. Images courtesy of Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, PA, USA.

MCI and Alzheimer's Disease Neurostructural Correlates (*NEURORADIOLOGY*)



Whitwell, Brain 2007

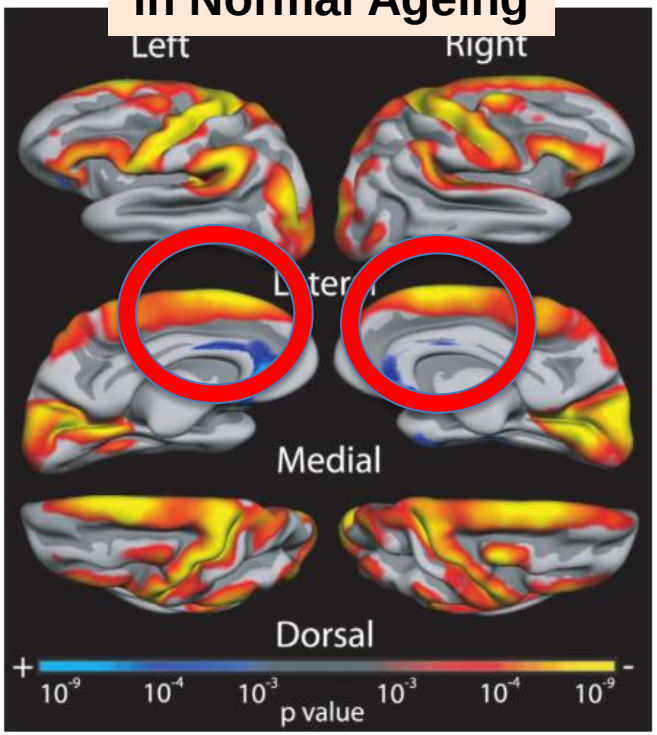
36 months to conversion 12 months to conversion Conversion

Mild Cognitive Impairment

Alzherimer's

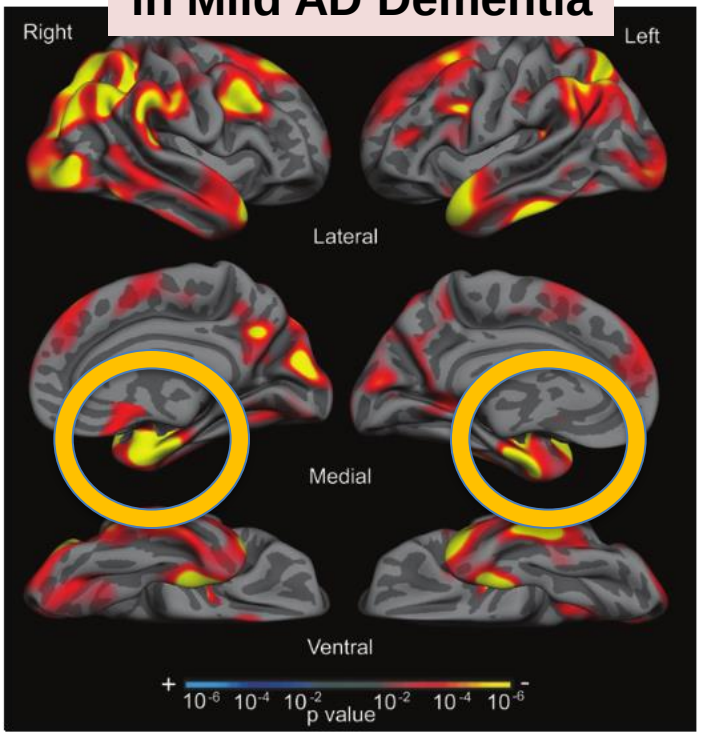
MCI and Alzheimer's Disesase Neurostructural Correlates

Cortical Thinning in Normal Ageing



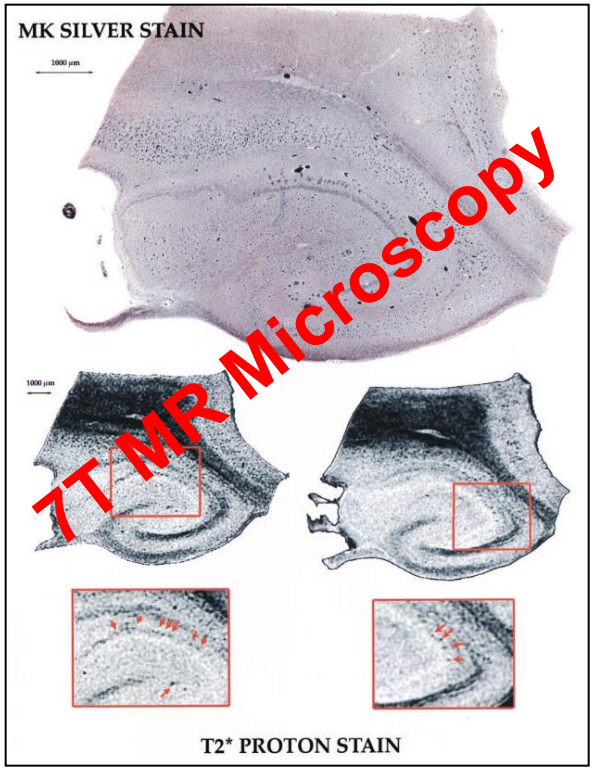
Salat, Cereb Cortex 2004

Cortical Thinning in Mild AD Dementia



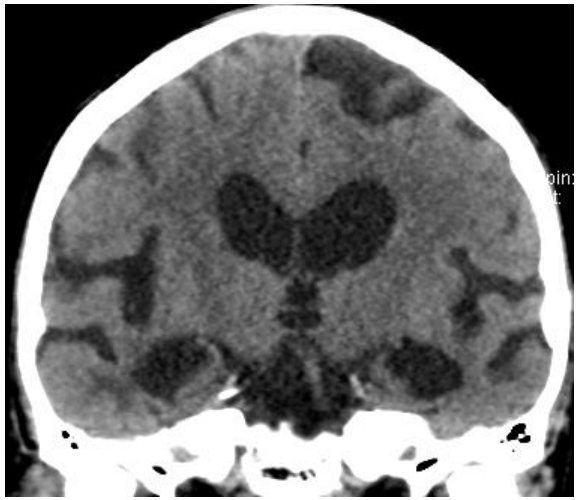
Dickerson, Cereb Cortex 2009

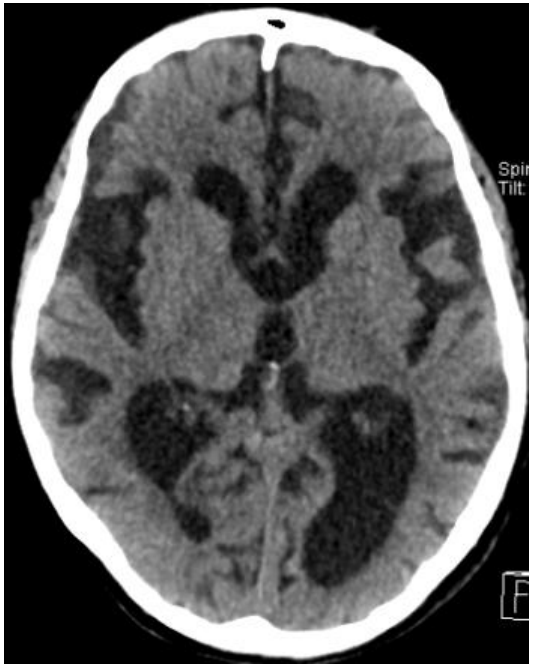
Alzheimer's Disesase Neurostructural Correlates
(Single subject Level)

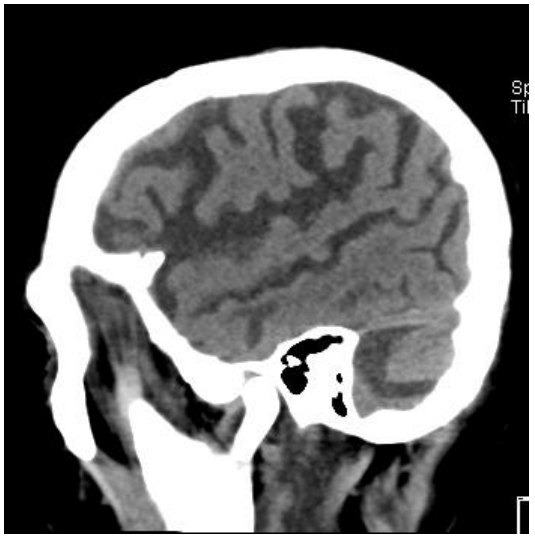


- ✓ Best structural imaging Modality: MRI
- ✓ However, Good-quality MD-CT *might* allow acceptable demonstration of Medial Temporal Atrophy (MTA)
- ✓ MTA is sensitive but not specific for AD!
- ✓ White Matter (WM) Gliosis seen in advanced stages
- ✓ Associated WM (Micro)vascular pathology may significantly reduce clinical threshold!

Clinical Routine: Is it a valuable Cost / Effectiveness Compromise?

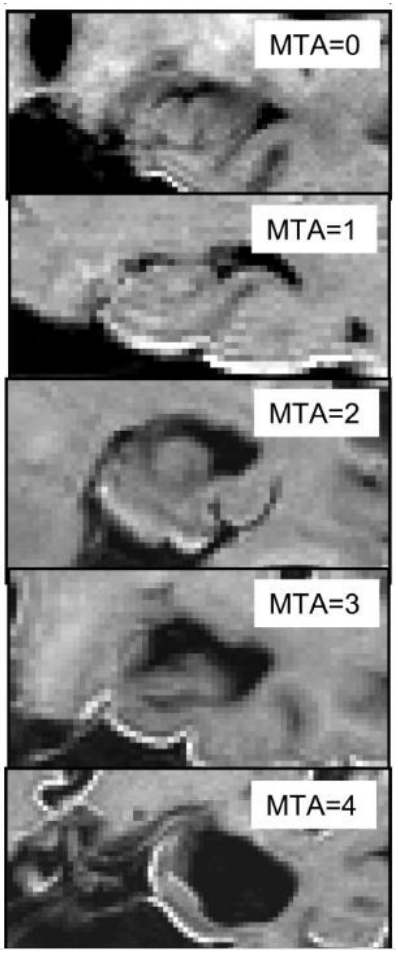






Alzheimer's Disesase Neurostructural Correlates
(Single subject Level)

Barkhof, Neurology 2007



sensitivity 85%
specificity 88%

MTA Score:

0: no atrophy
1: only widening of choroid fissure
2: also widening of temporal horn of lateral ventricle
3: moderate loss of hippocampal volume (decrease in height)
4: severe volume loss of hippocampus

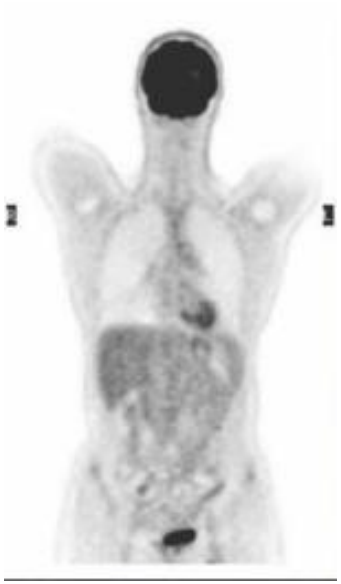
< 75 years: score 2 or more is abnormal.
> 75 years: score 3 or more is abnormal.

Pros:
- ✓Easy to perform (Visual-based, Conventional MRI)
- ✓Single subject
- ✓Reproducibility
- ✓Sensitive to degenerative hippocampal pathology (AD+++)
- ✓Good predictor of dementia

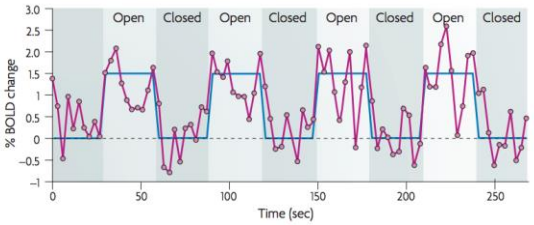
Cons:
- ▪Not Specific for AD! (DDx: Vascular Dementia, FTD, Lewy-related, etc)

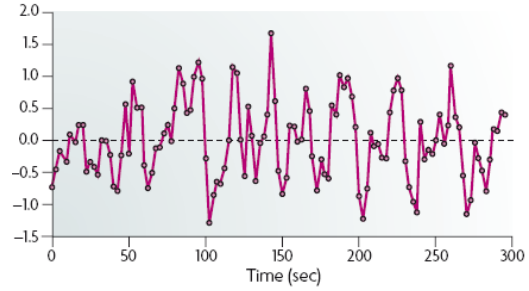
Attività spontanea

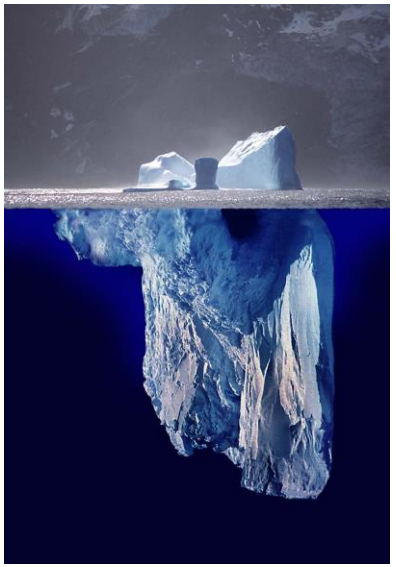
Dell' energia consumata dal corpo
20% Cervello
(2% Peso Corporeo)



Dell' energia consumata dal cervello
Attività Evocata 5-10%





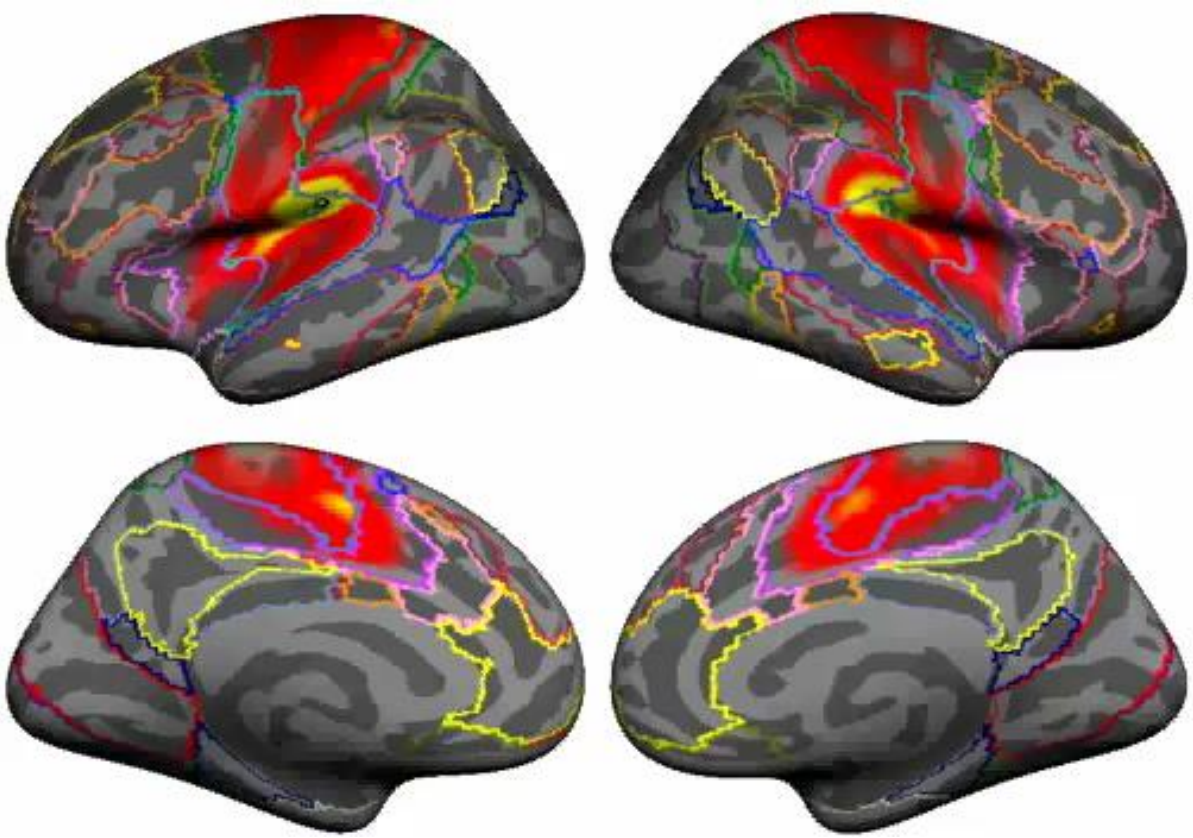


Attività Spontanea 70-80%

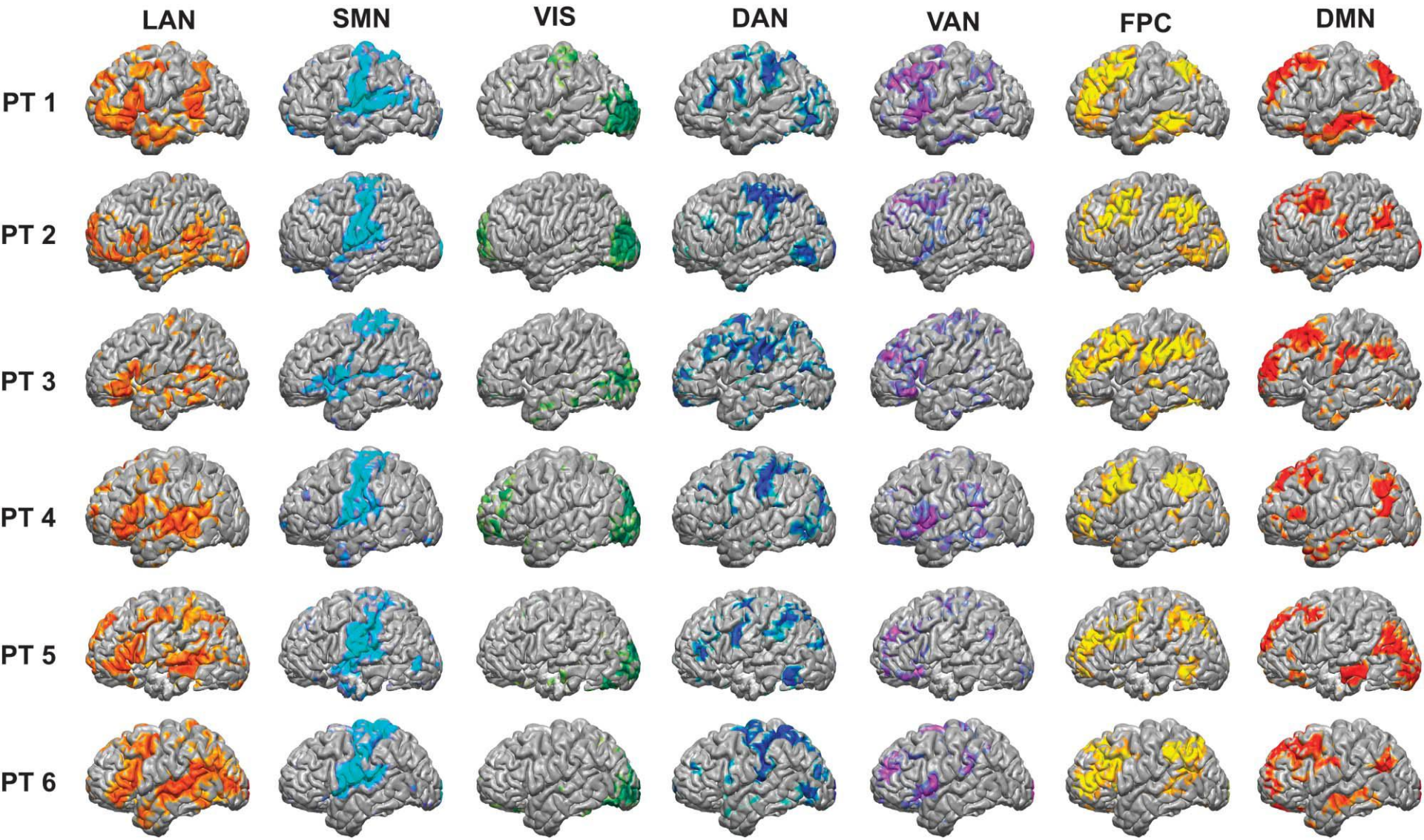
L' attività spontanea BOLD rappresenta la frazione maggiore dell' attività funzionale del cervello. Non è rumore casuale ma attività organizzata in maniera spazialmente specifica.

Raichle & Mintun 2006; Annu Rev Neurosci

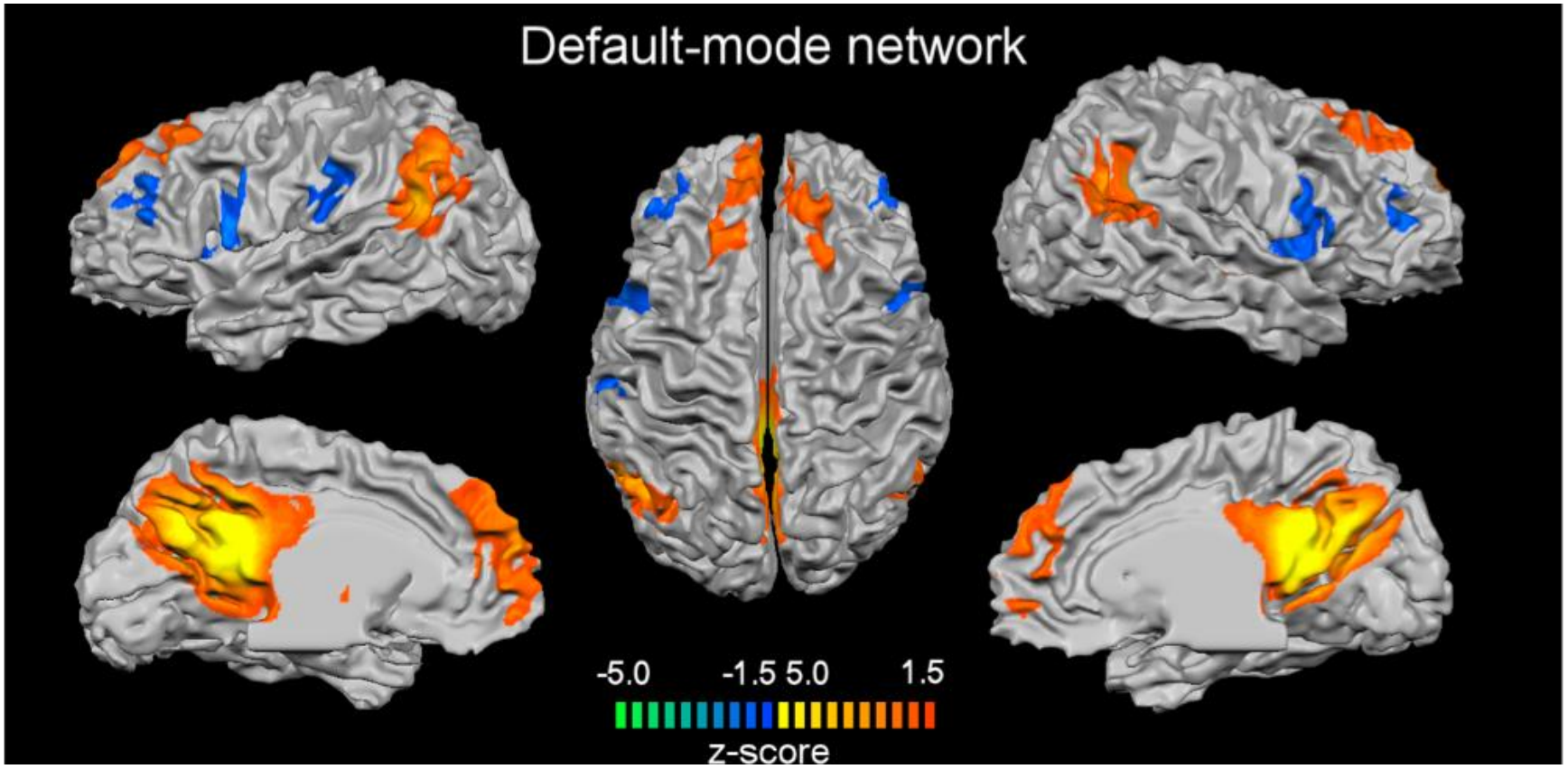
fcMRI



Yeo et al. 2011



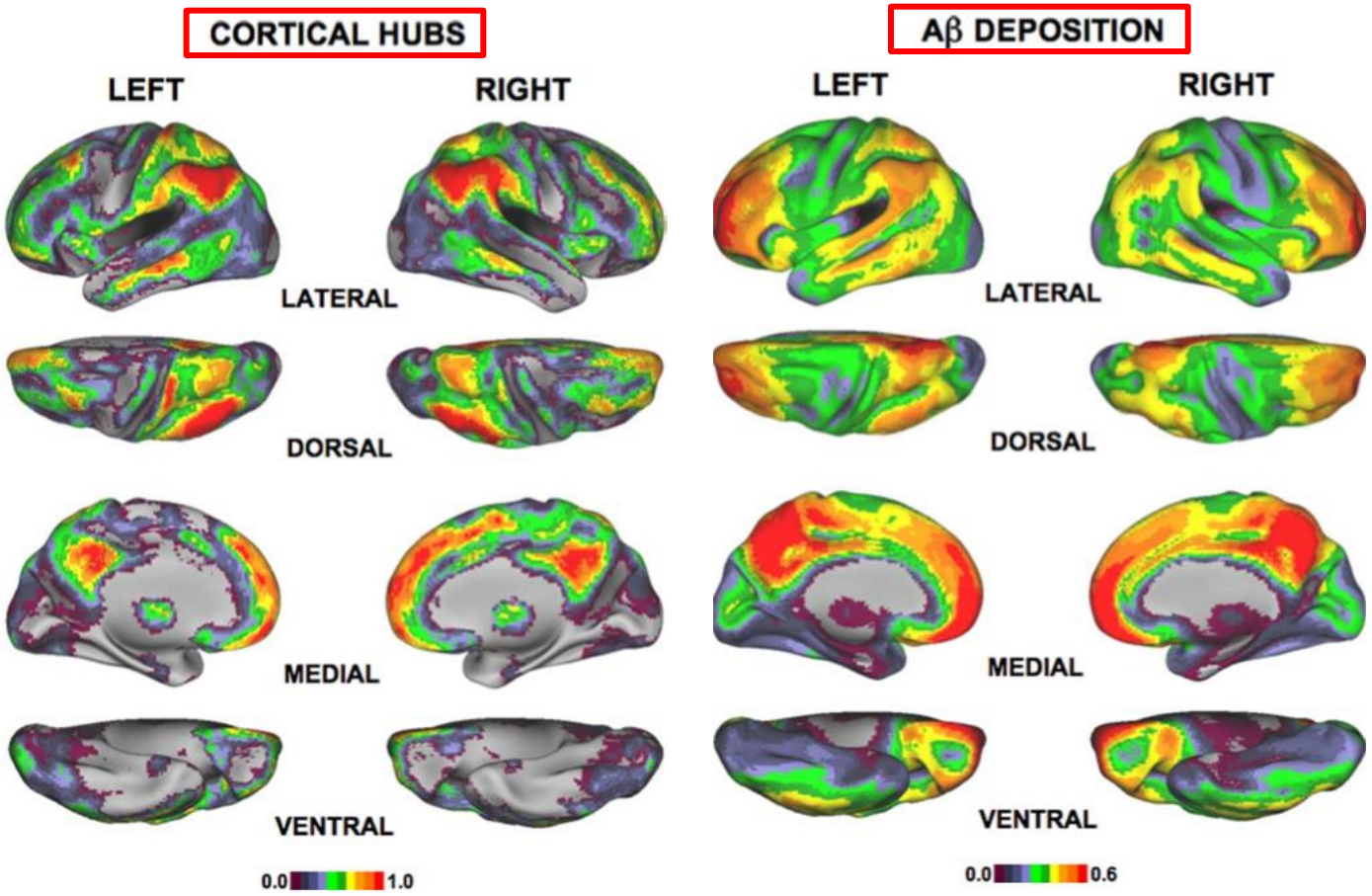
Timothy J. Mitchell et al. 2013



Set of brain regions that are more active during passive task conditions than during numerous goal directed task conditions
[Shulman, 1997; Raichle, 2001]

Network of brain regions showing significant functional connectivity during resting state [Greicius, 2003]

Aβ deposition in Alzheimer's disease occurs preferentially in the locations of cortical hubs of the DMN



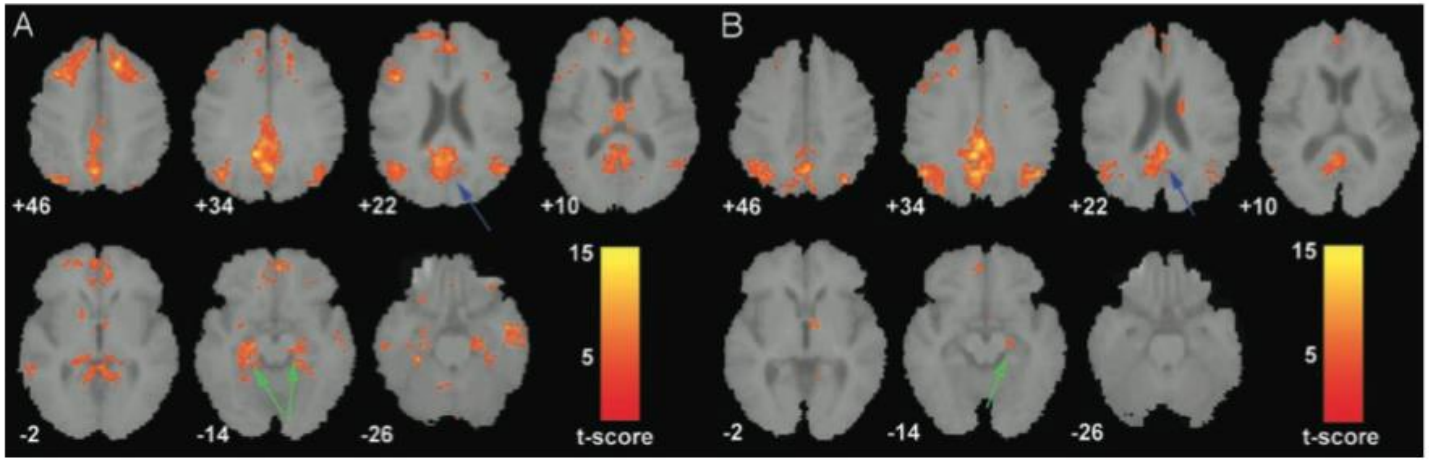
Buckner et al. 2009

Functional connectivity and neurodegenerative disorders

- Functional network disruption as assessed with resting-state functional MRI demonstrates distinct patterns of network disruption across the major neurodegenerative diseases
- These network abnormalities are somewhat specific to the clinical syndromes and, in Alzheimer's disease and fronto-temporal dementia, network disruption tracks the pattern of pathological changes
- These findings might have practical implications for diagnostic accuracy, allowing earlier detection of neurodegenerative diseases even at the presymptomatic stage, and tracking of disease progression.

AD Neuro*functional* Correlates *(Group Level)*

- Disruption of default-mode- network regions in Alzheimer's disease has been consistently reported in resting-state fMRI studies



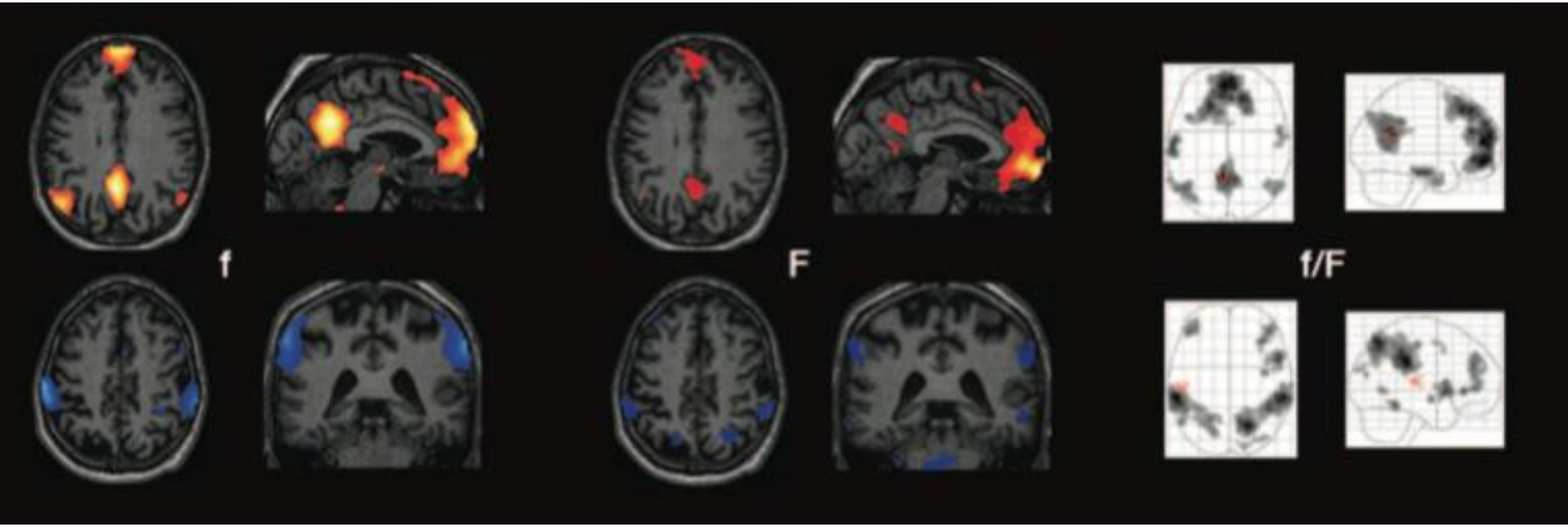
Greicius et al. 2003

Healthy Controls AD Patients

Default Mode Network (FC-MRI)

MCI

- Similar changes have been reported in people with mild cognitive impairment, a condition that clinicians believe often represents preclinical Alzheimer's disease



DMN in: healthy elderly MCI subjects

Sorg et al. 2007

A look at some «real-world» **SINGLE SUBJECT** data

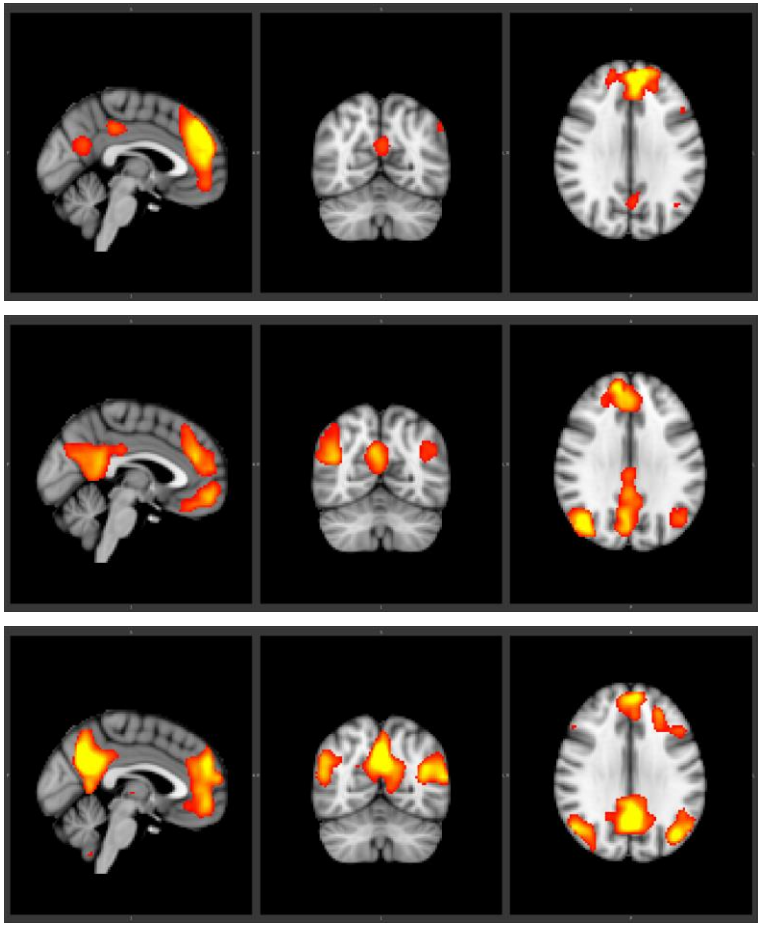
MCI PIB+, CSF+ (= early AD)
CDR-SB 0.5 (molto lieve)
MMSE>24

#1, 69y/o

#2, 70y/o

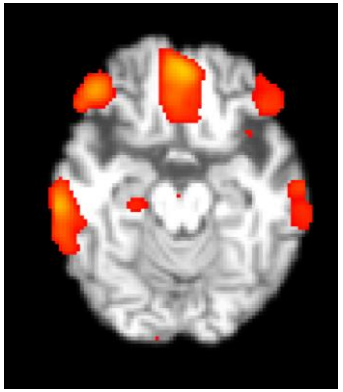
HC

#3, 71y/o



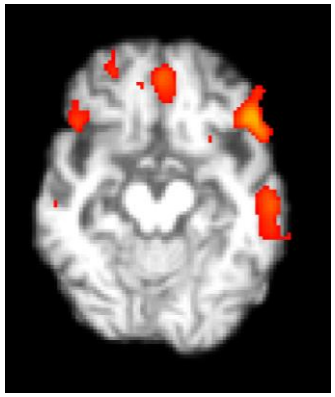
z-score range: 4 - 10

A look at some «real-world» **SINGLE SUBJECT** data



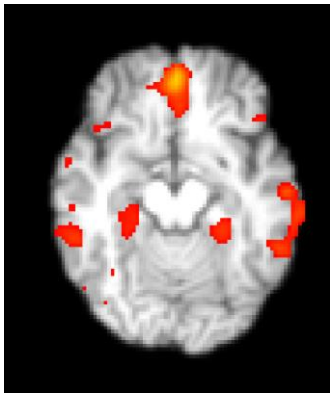
1

Early AD



2

Early AD



3

HC

z-score range: 4 - 10

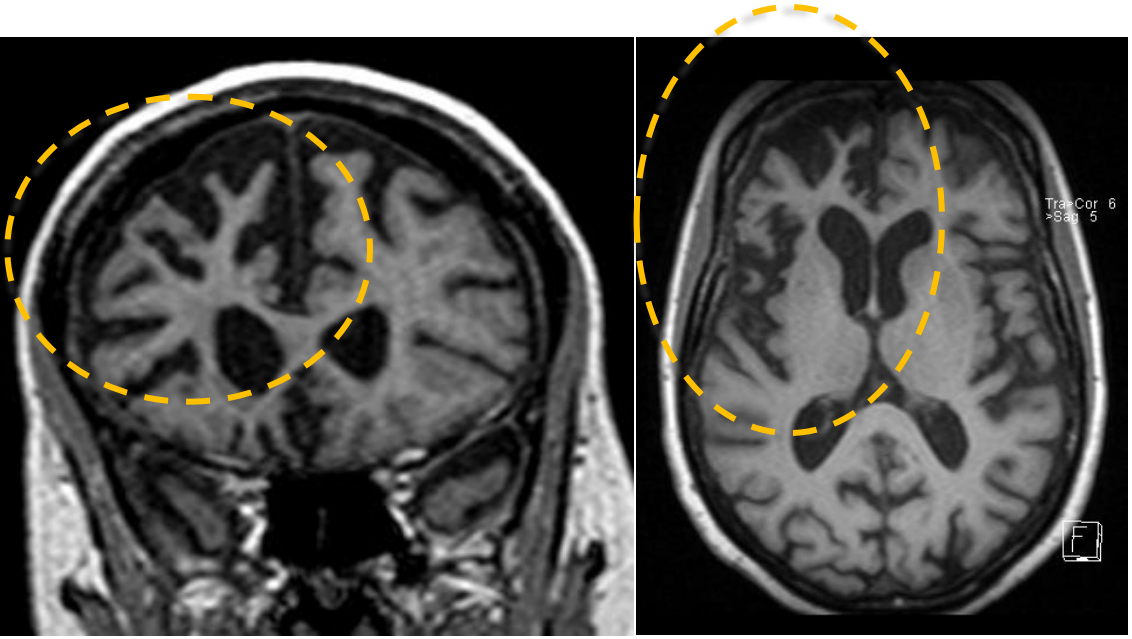
Riccardo Navarra, PhD
ITAB - Chieti

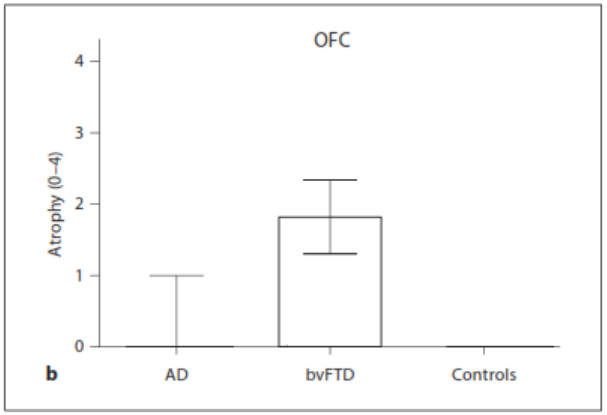
Fronto-temporal dementia

FTD refers to a group of clinical syndromes associated with underlying fronto-temporal lobar degeneration:

1. behavioural variant (bvFTD), which presents with social–emotional dysfunction
2. two primary progressive aphasia (PPA) subtypes: the semantic and nonfluent/agrammatic variants
3. logopenic variant (many patients with this variant show underlying Alzheimer's disease at autopsy)

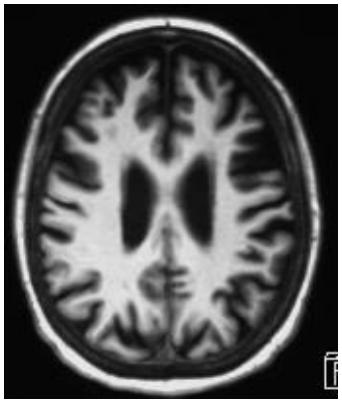
Behavioral variant (bvFTD)

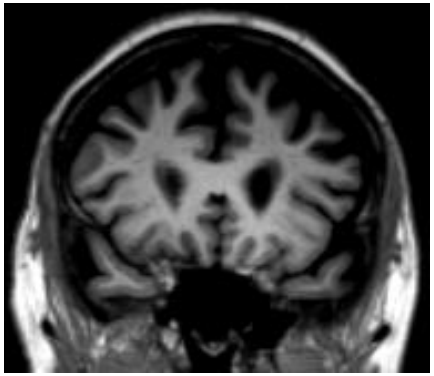


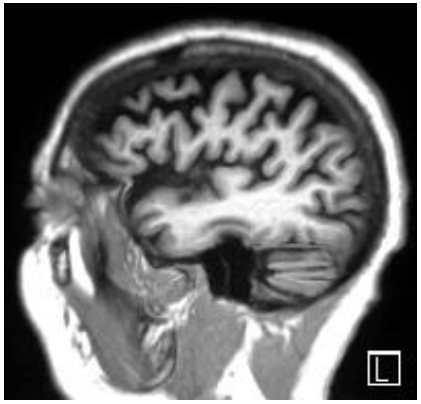


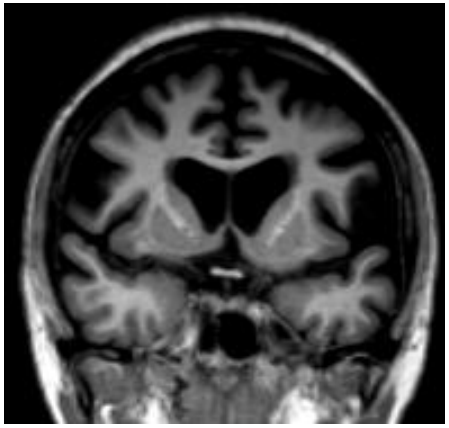
Hornberger, Dement Geriatr Cogn Disord 2010

Orbito-frontal atrophy ddx to AD

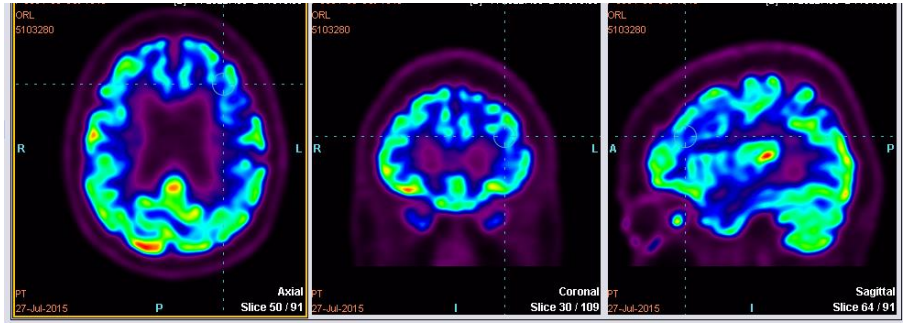








FDG-PET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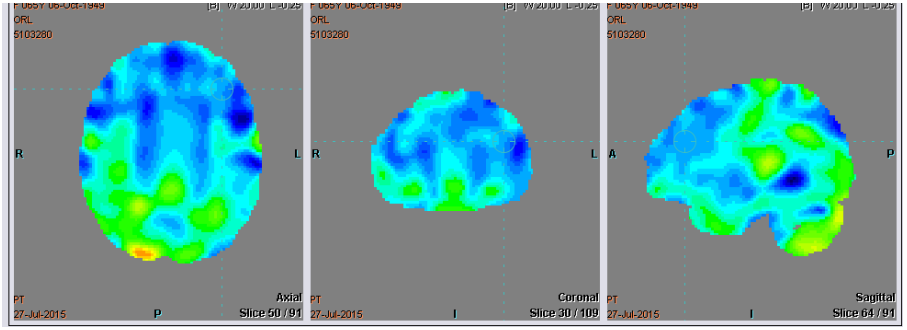
Slice 64 / 91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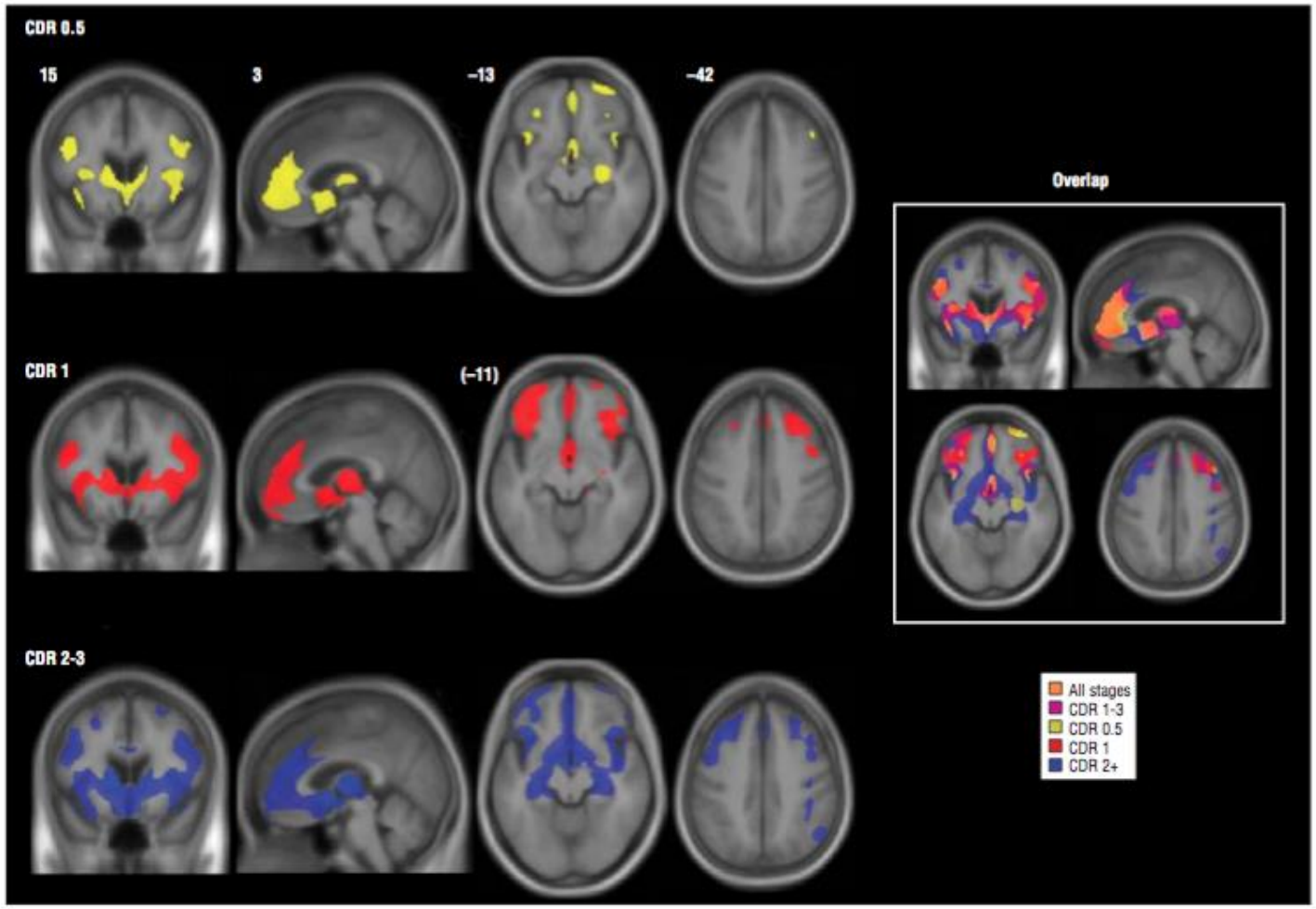
Clinical stage-specific (CDR) Gray Matter atrophy in bvFTD

(*Group Level*)



Seeley et al. 2008

FTLD/PPA Neurostructural Substrates

- Relatively **low specificity of Neuroradiological methods** to classify bvFTD/PPA(PNFA, sFTD, LP)/AD phenotypes (**single-subject level**) reflects the **wide overlap** between **neuropathological and behavioural** findings

- **Variability in the patterns of distribution and spread over time** of abnormal protein deposits characterize **different networks impairment** and, ultimately, behavioral phenotypes

- Nevertheless, **PPA patients,** either classified by language domains performance or clinical diagnosis (e.g. Gorno-Tempini), showed **distinct patterns of peripheral grey matter atrophy**.

Semantic / Non-Fluent / Logopenic Variants (sFTD, PNFA, LP)

Language Domains – Based Classification (*Group-Level*)

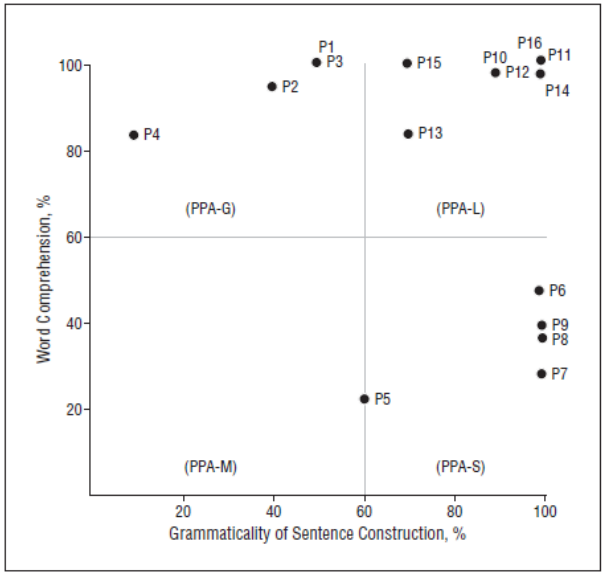
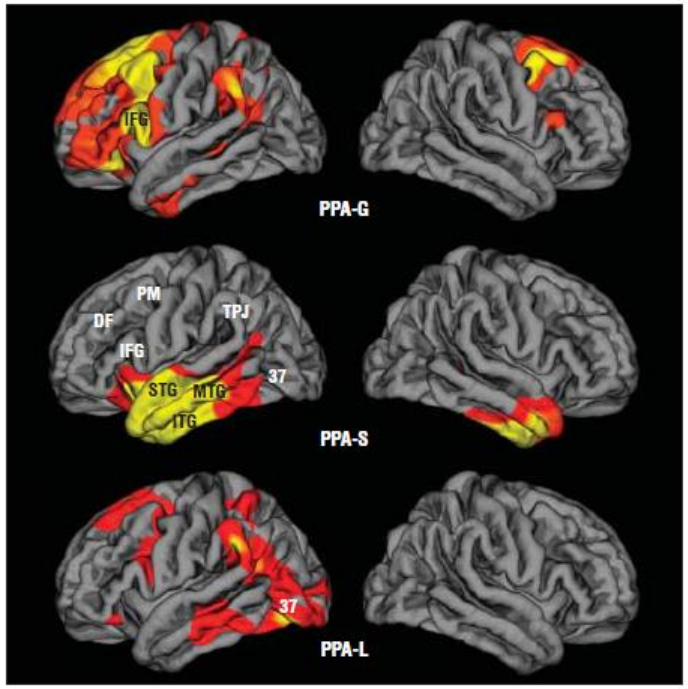


Figure 2. A 2-dimensional template based on single-word comprehension (Peabody Picture Vocabulary Test—Fourth Edition) and grammatical structure of sentences (Northwestern Anagram Test). The 60% performance level divides the template into 4 quadrants, 1 for each primary progressive aphasia (PPA) subtype (PPA-G, agrammatic variant; PPA-S, semantic variant; PPA-M, mixed variant; and PPA-L, logopenic variant). The values on the x- and y-axes reflect the performance percentages shown in Figure 1. P1-P16 indicate patients 1 to 16.

L



Non fluente

Semantica

Logopenica

Mesulam, Arch Neurol 2009

Neurodegenerative Diseases Target Large-Scale Human Brain Networks

William W. Seeley,[1,*] Richard K. Crawford,[1] Juan Zhou,[1] Bruce L. Miller,[1] and Michael D. Greicius[2]
[1]Memory and Aging Center, Department of Neurology, University of California, San Francisco, San Francisco, CA 94143, USA
[2]Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA
*Correspondence: wseeley@memory.ucsf.edu
DOI 10.1016/j.neuron.2009.03.024

In summary, neurodegenerative diseases are not diffuse, random, or confluent, but instead target specific large-scale distributed networks. In the healthy brain, these networks feature convergent intrinsic functional and structural covariance. To build more comprehensive disease pathogenesis models, neurodegeneration researchers should pursue the interface between disease protein aggregation and selective, network-driven neuronal vulnerability.

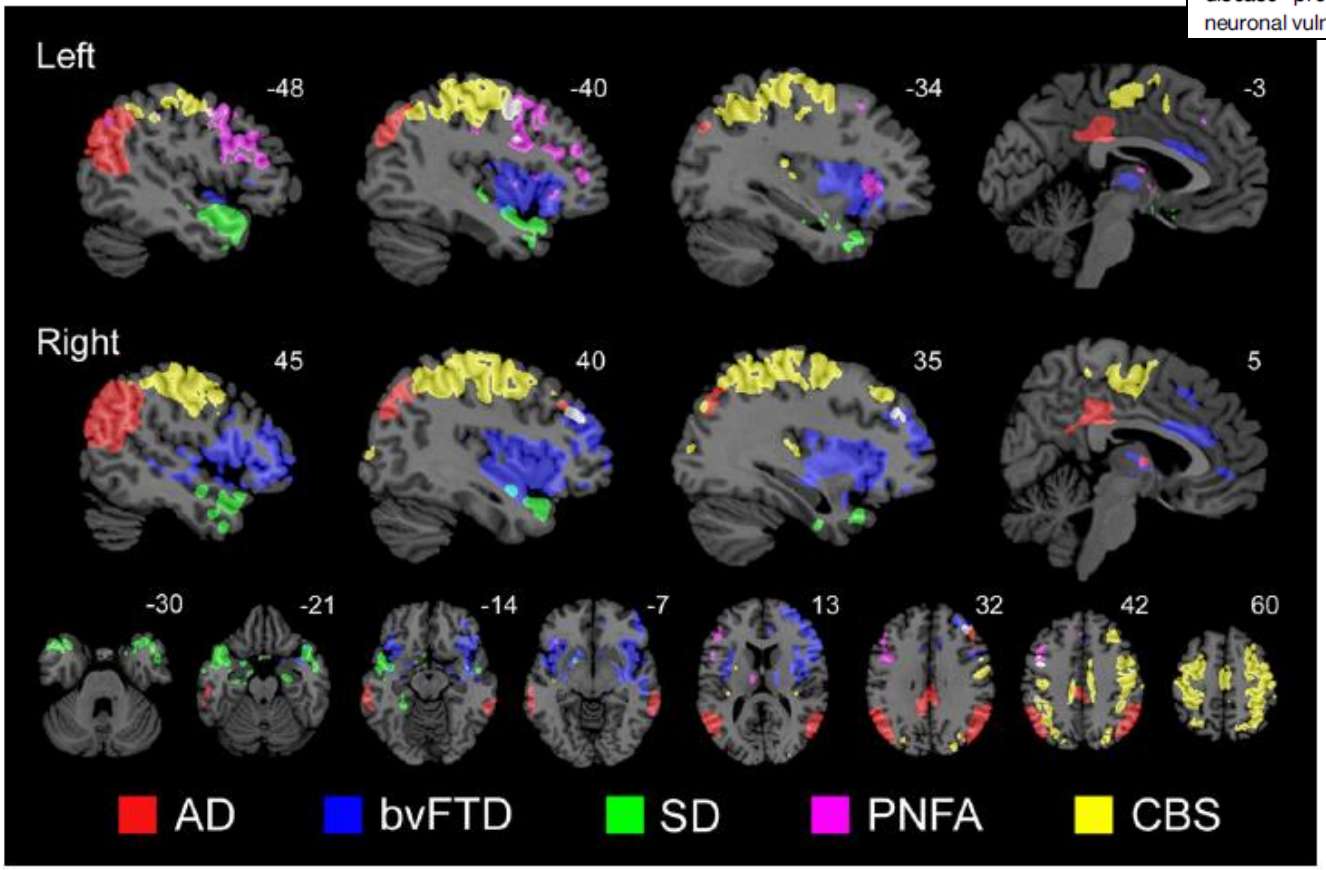


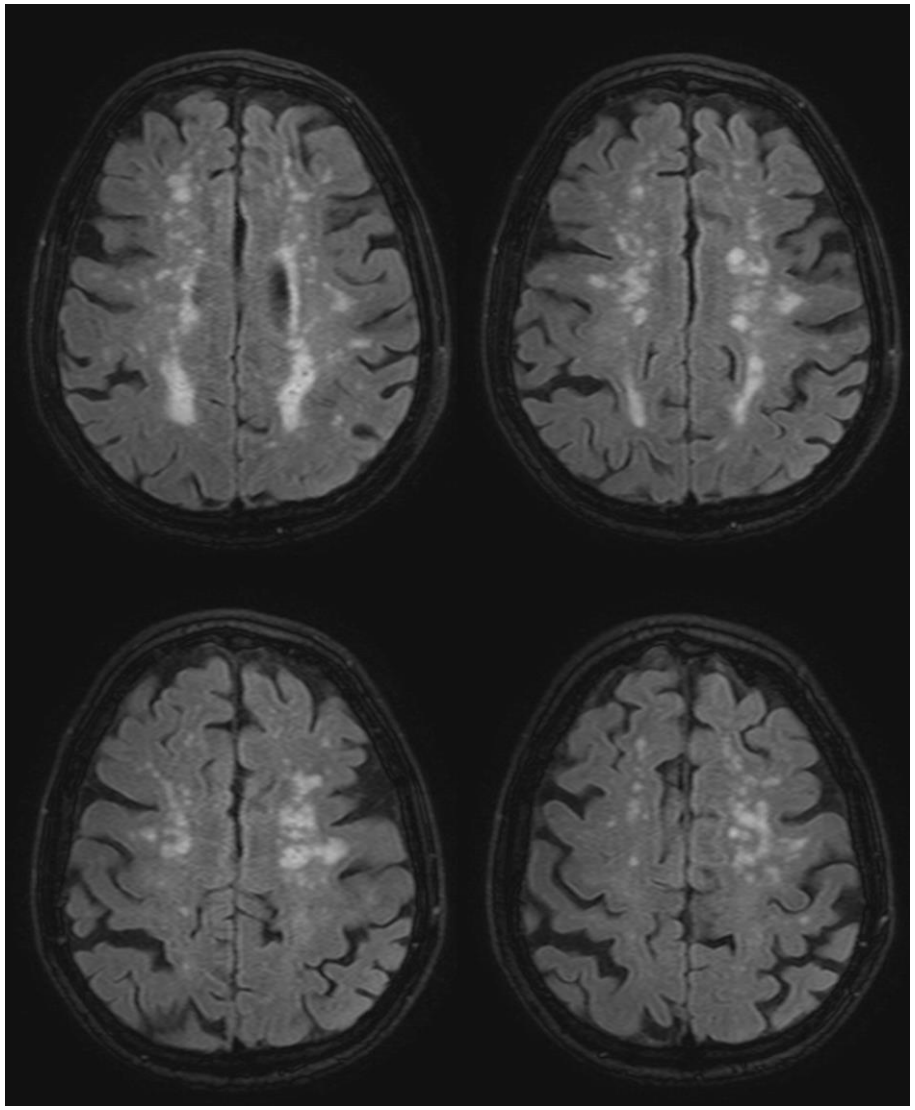
Figure 6. Neurodegenerative Syndromes Target Anatomically Dissociable Brain Systems

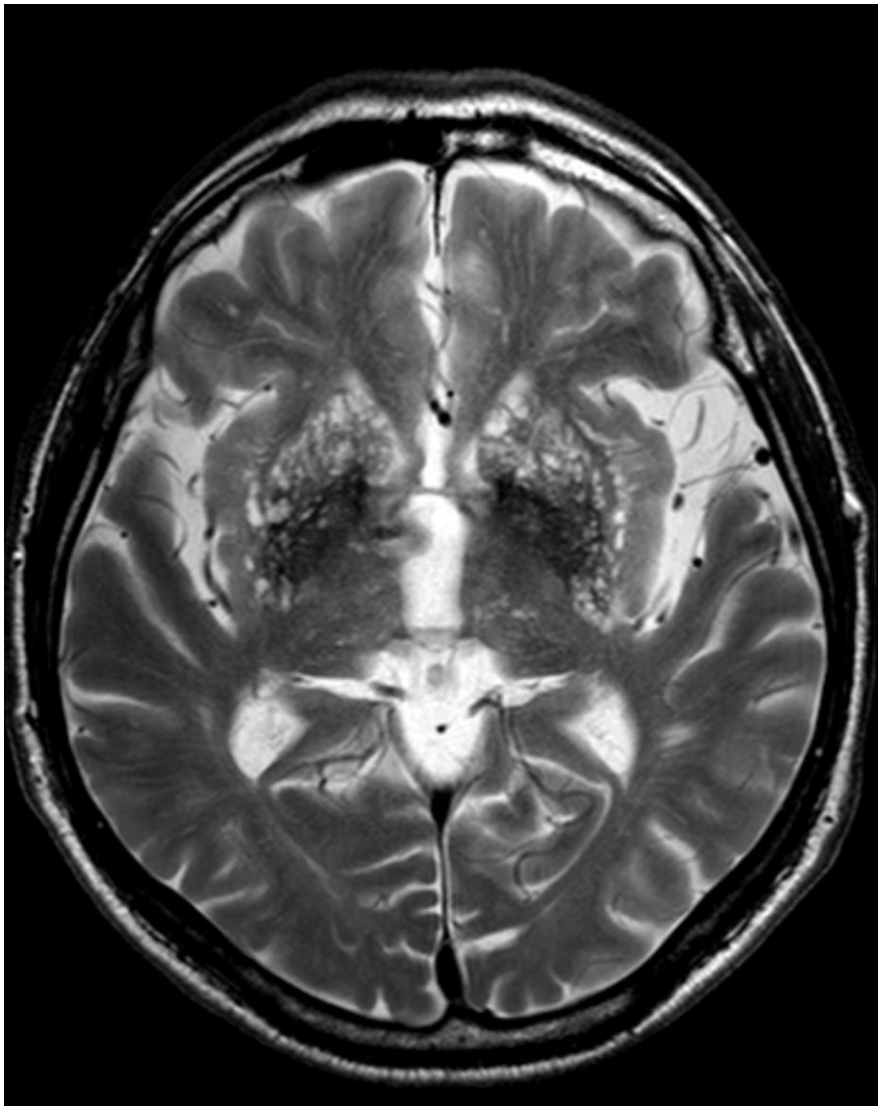
Colored regions highlight voxels found within associated maps of syndromic atrophy ($p < 0.0001$, uncorrected; patients versus controls), intrinsic functional connectivity (ICA-derived; $p < 0.01$, corrected; healthy controls only), and structural covariance ($p < 0.0001$, uncorrected; healthy controls only). The color code (bottom) refers to the atrophy map used to derive the relevant seed ROI. These results, statistically thresholded to inflate potential overlap across the five three-map data sets, illustrate the dissociable nature of the targeted brain systems.

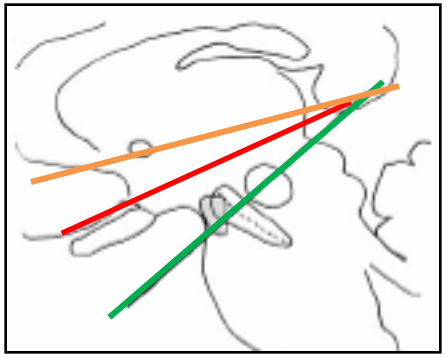
PARKINSON E PARKINSONISMI
Neuroradiologia

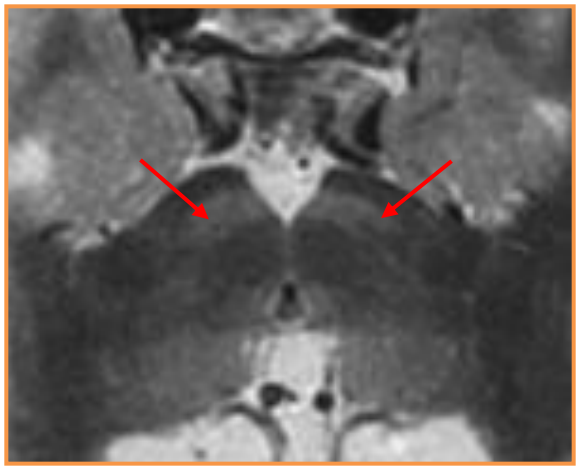
- Escludere una MSA o un'altra possibile causa di parkinsonismo secondario (vascolare, idrocefalo, tumori)
- Nelle forme idiopatiche TC ed RM sono generalmente normali

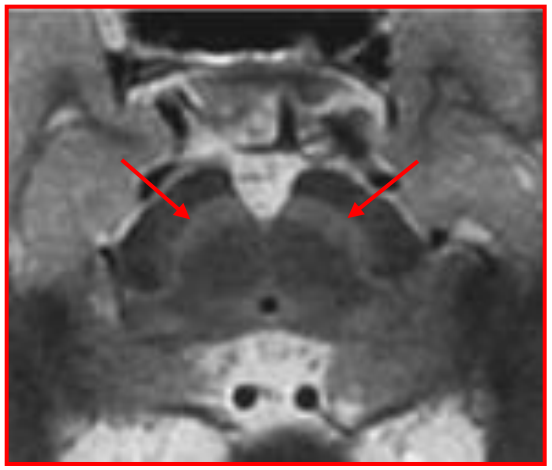
Parkinsonismo vascolare

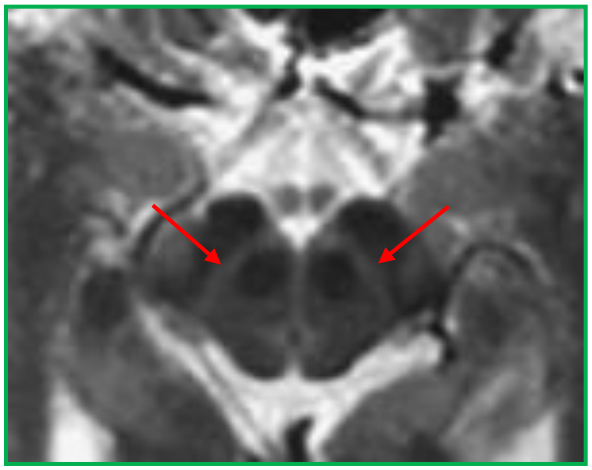


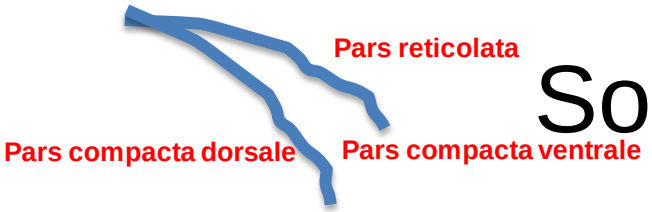












Sostanza nera a 7T

M. Cosottini et al. Radiology 2014

HC

PD

c1

a

b

c

d

e

Level I

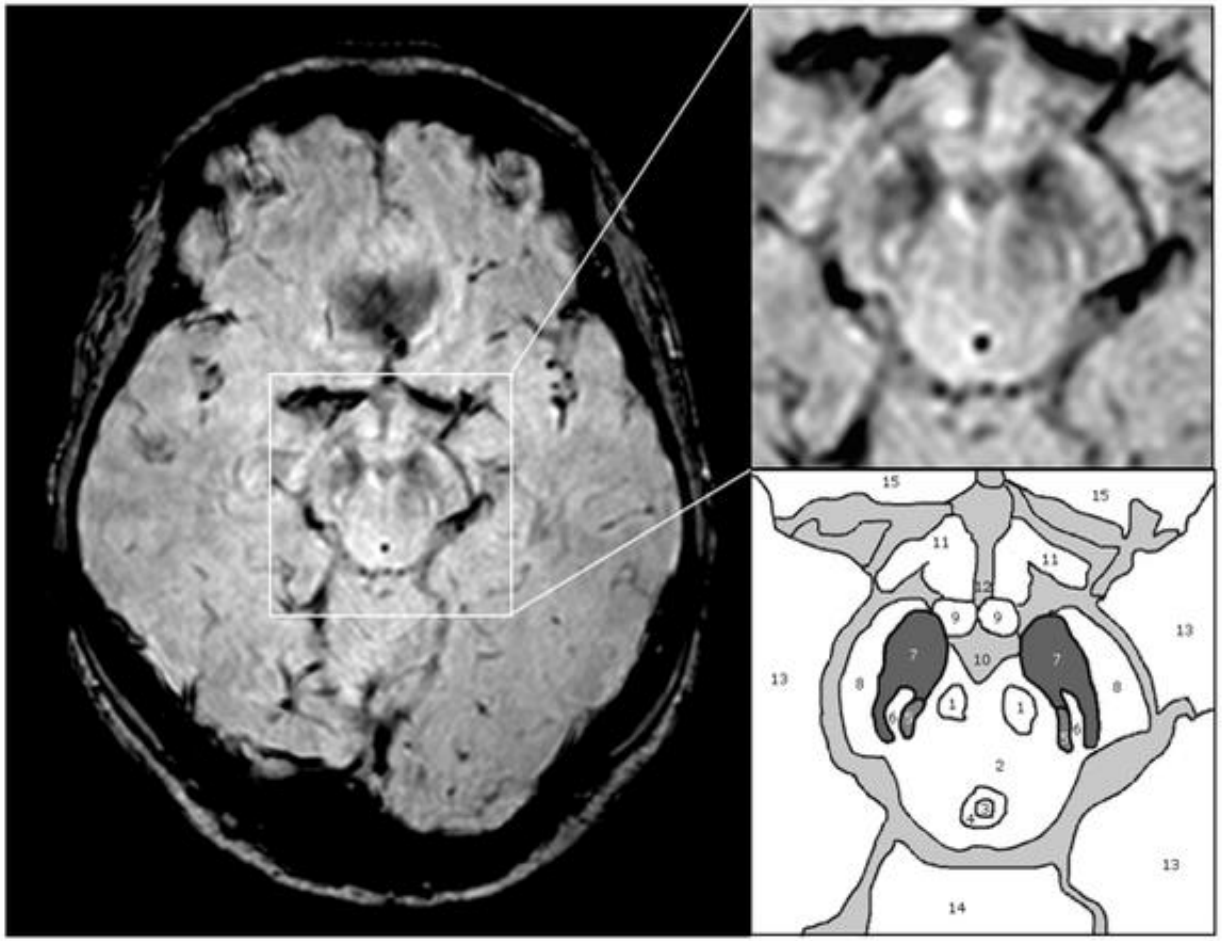
Level II

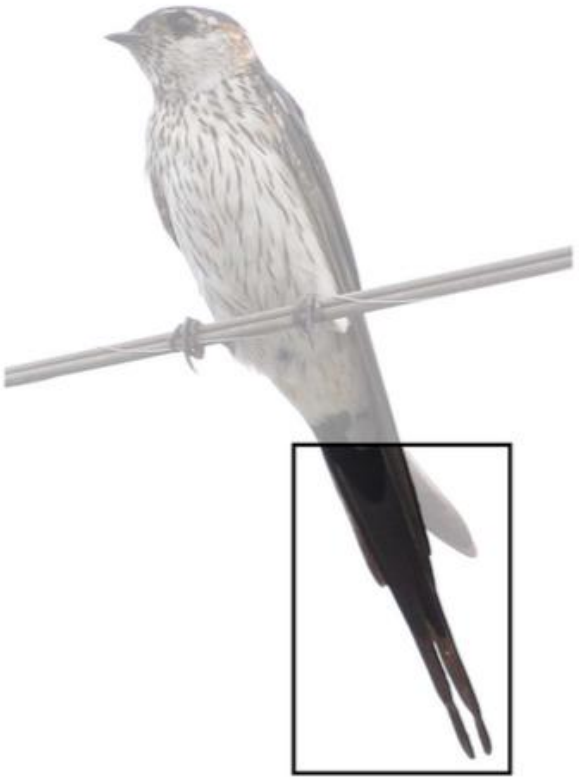
Level III

Sensibilità 100%; Specificità 96%

Ma anche a 3T

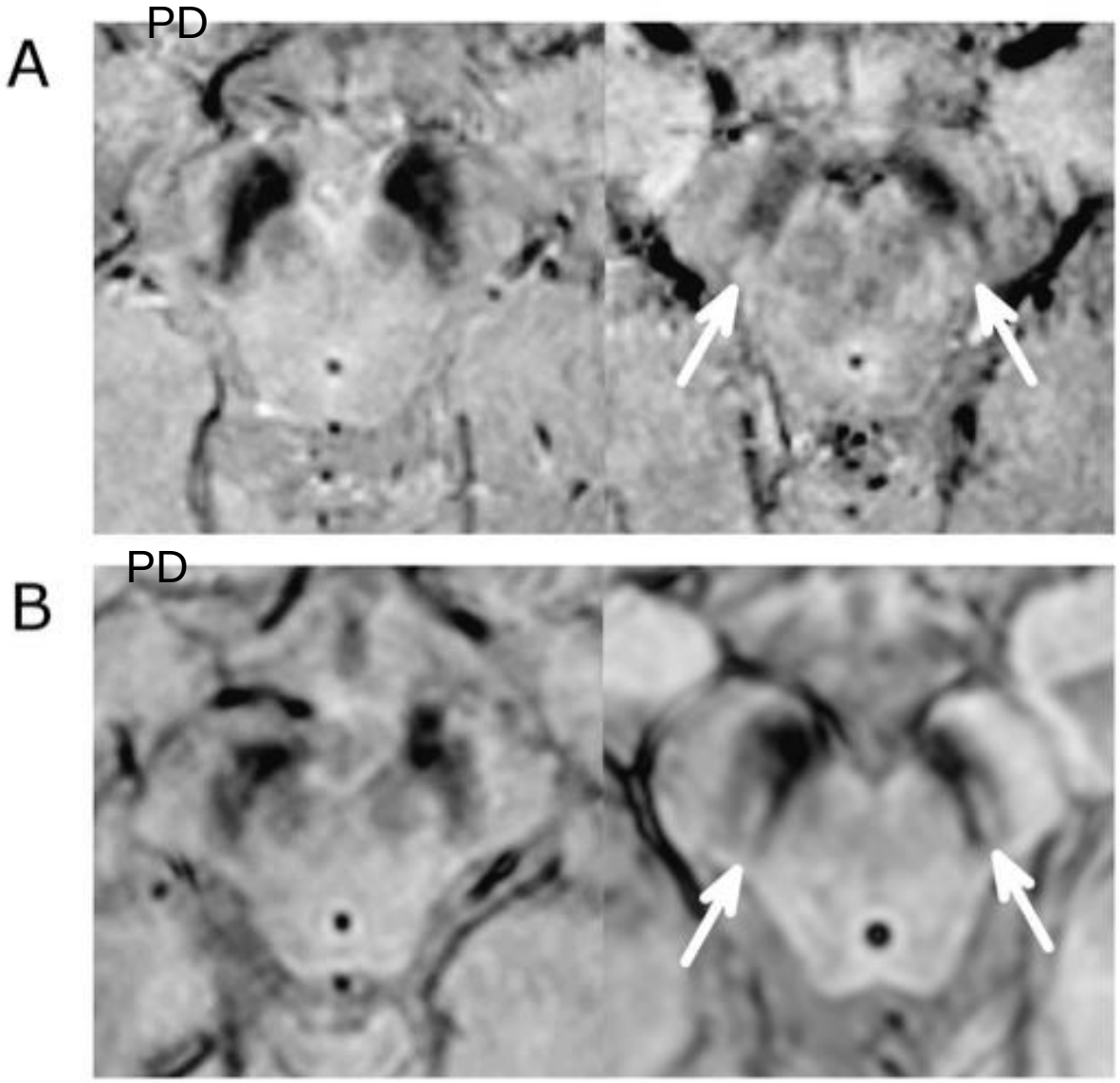
S. Schwarz et al. 2014





Ma anche a 3T

S. Schwarz et al. 2014



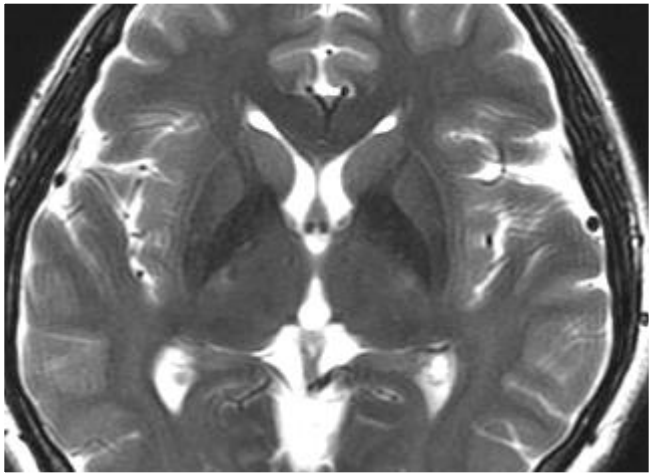
Caratteristiche RM della MSA (Deg. nigro-striatale; Deg. Autonomica; OPCA)

- Supratentorial (Deg. nigro-striatale; Deg. Autonomica)
  - Putaminal atrophy
  - Dorsolateral hypointensity in the putamen
  - Linear slit-like hyperintensity in the lateral margin of putamen on T2WI
- Infratentorial (OPCA)
  - Atrophy of brain stem, middle cerebellar peduncle, cerebellum
  - Hyperintensities in the pons, middle cerebellar peduncle, cerebellum (Hot cross bun sign)

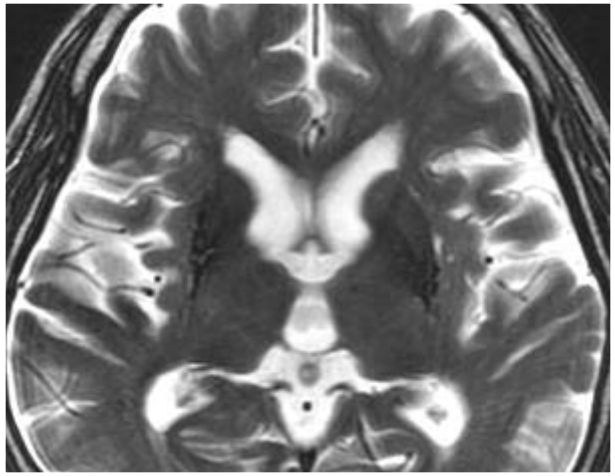
→ Specific parameters for MSA-P

(Savoiardo, 1990; Schrag, 2000, Nicolleti, 2006)

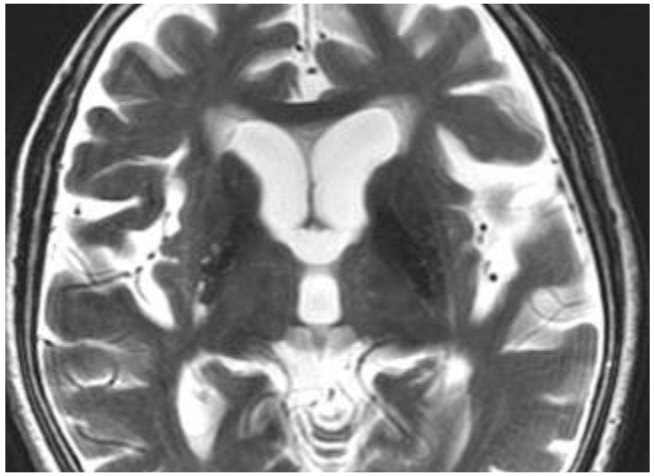
Atrofia del Putamen



Absent



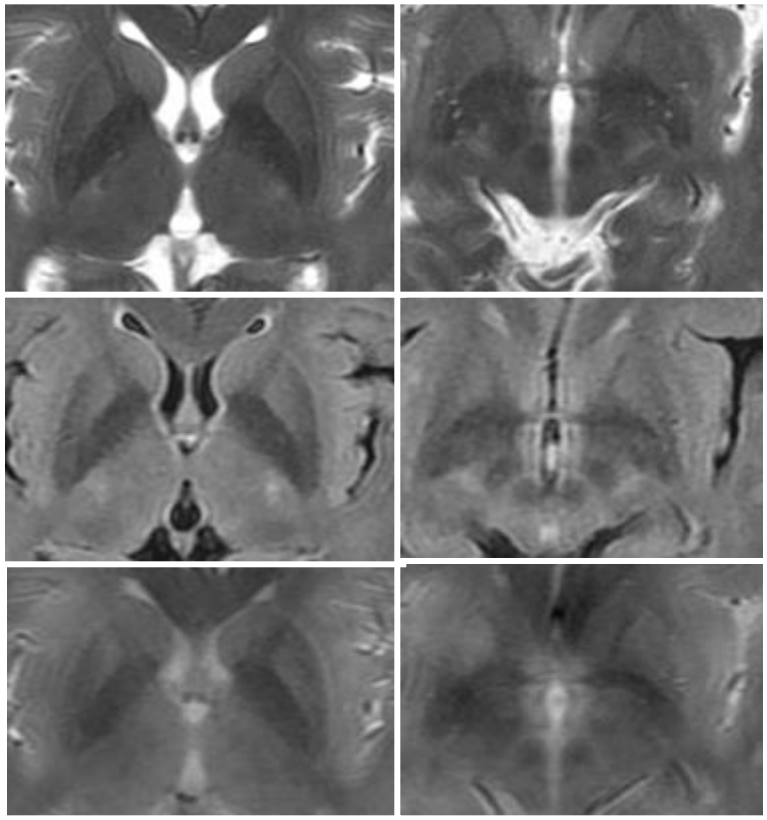
Present, Both, (Rt>Lt)



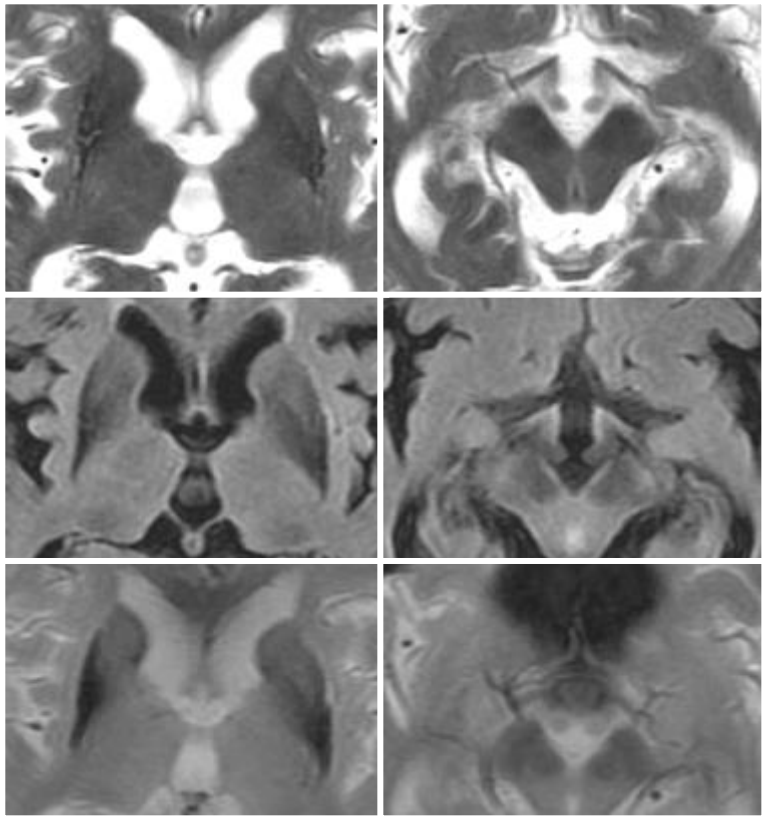
Present, Rt

Il parametro RM più specifico per distinguere MSA da PD

Ipointensità T2 dorso-laterale del Putamen



Grade 1 at all sequences

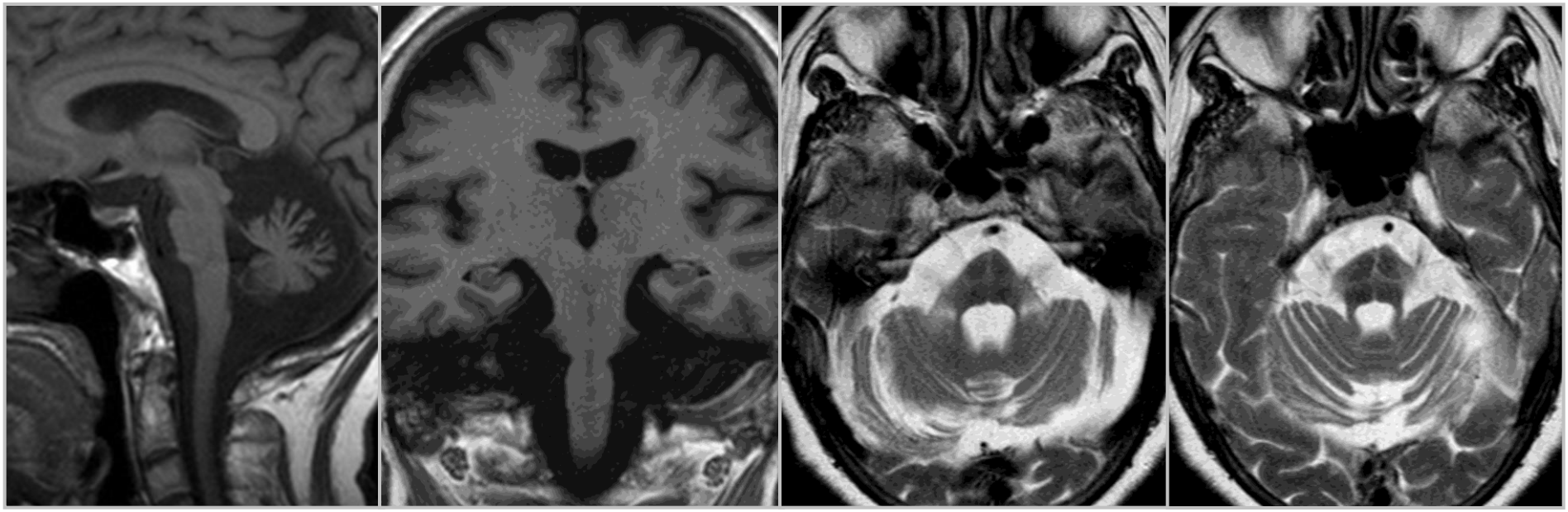


Grade 3 at all sequences

Bassa sensibilità, bassa specificità

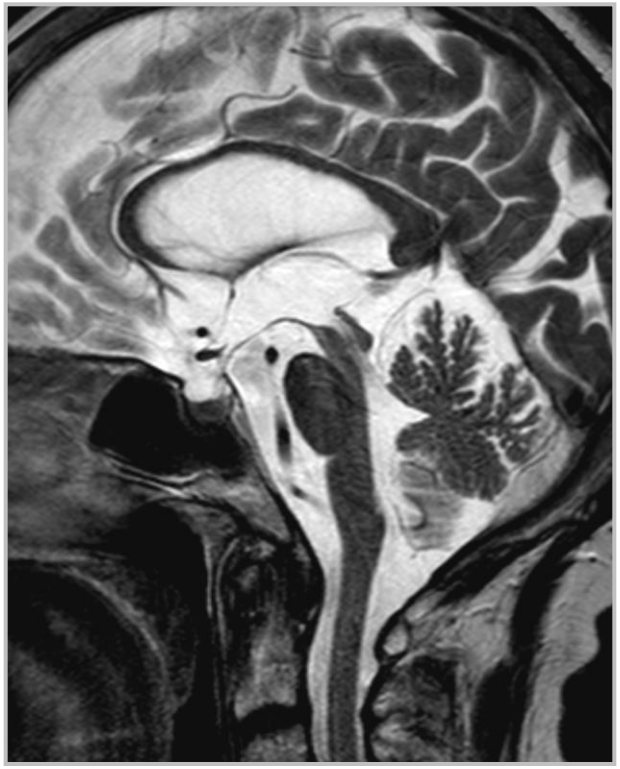
Atrofia olivo-ponto-cerebellare

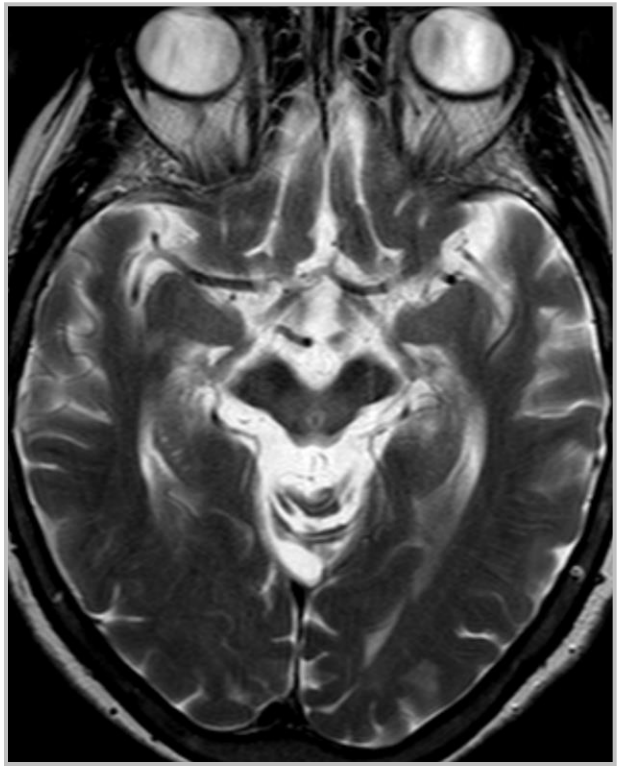
- Atrofia del ponte e degli emisferi cerebellari (relativo risparmio del verme)
- Iperintensità in T2 delle fibre trasverse pontine, peduncoli cerebellari medi e delle olive bulbari

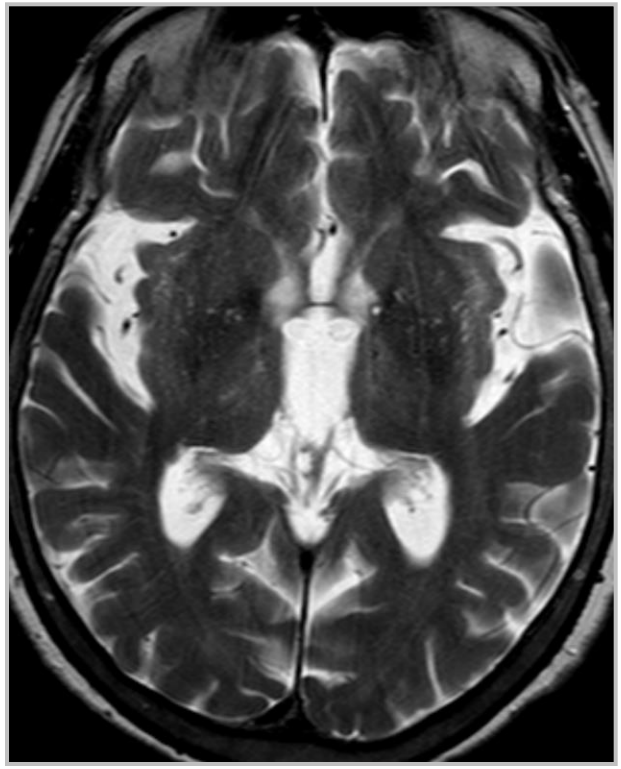


Paralisi sopra-nucleare progressiva

- Severa progressiva atrofia del mesencefalo, tetto e peduncoli cerebellari superiori
- Profilo superiore mesencefalico concavo
- Possibile iperintensità in T2 della sg periacqueduttale



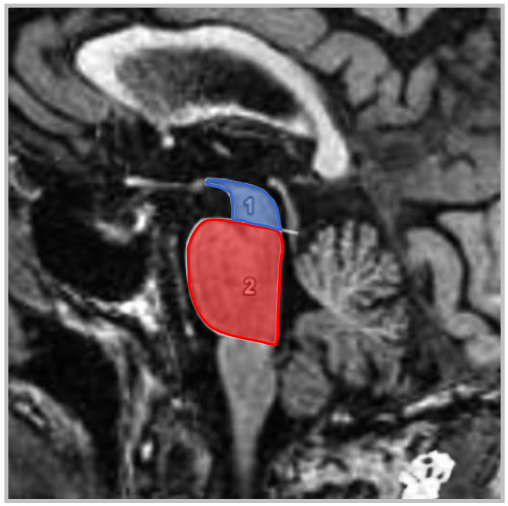


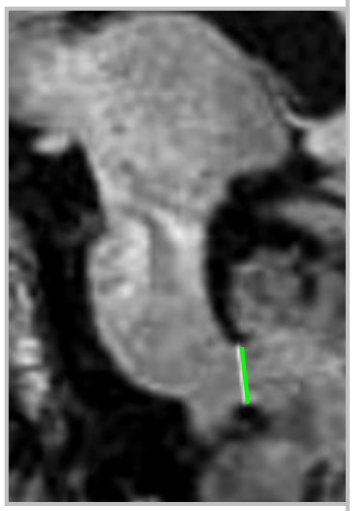


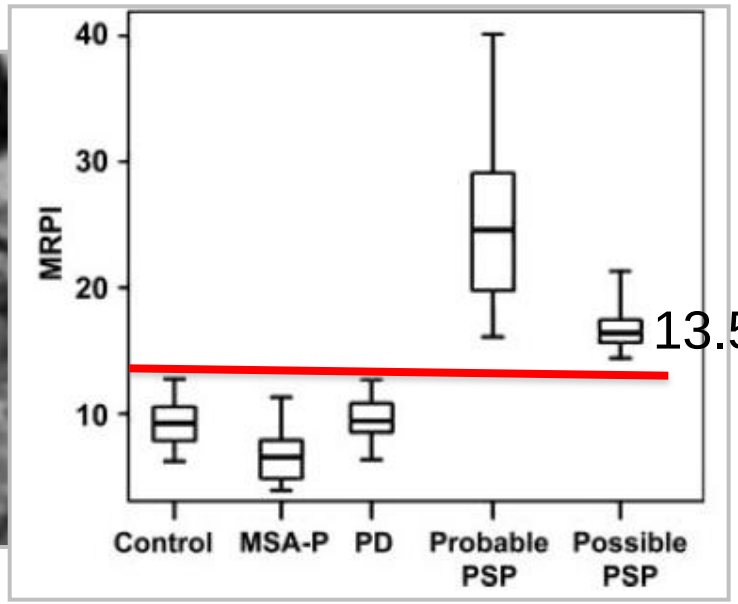
DDX

PD - MSA

MR Parkinson Index







(P/M) x (MCP/SCP)

The MR parkinsonism index can help distinguish patients with PSP from those with PD and MSA-P on an individual basis. Sens/Spec 100%

Quattrone A. et al.: *MR Imaging Index for differentiation of Progressive Supranuclear Palsy from Parkinson Disease and the Parkinson Variant of Multiple System Atrophy.* Radiology 246(1):214-221, 2008

MRI measurements predict PSP in unclassifiable parkinsonisms

A cohort study

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M. Salsone, MD
L. Giofrè, MD
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ABSTRACT

Objective: Magnetic resonance parkinsonism index (MRPI) has been proposed as a powerful tool to discriminate patients with progressive supranuclear palsy (PSP) from those with Parkinson disease (PD) or other parkinsonisms, on an individual basis. We investigated the usefulness of MRPI in predicting the clinical evolution in PSP of patients with clinically unclassifiable parkinsonism (CUP), i.e., parkinsonism not fulfilling the established clinical diagnostic criteria for any parkinsonian disorders, using a cohort study.

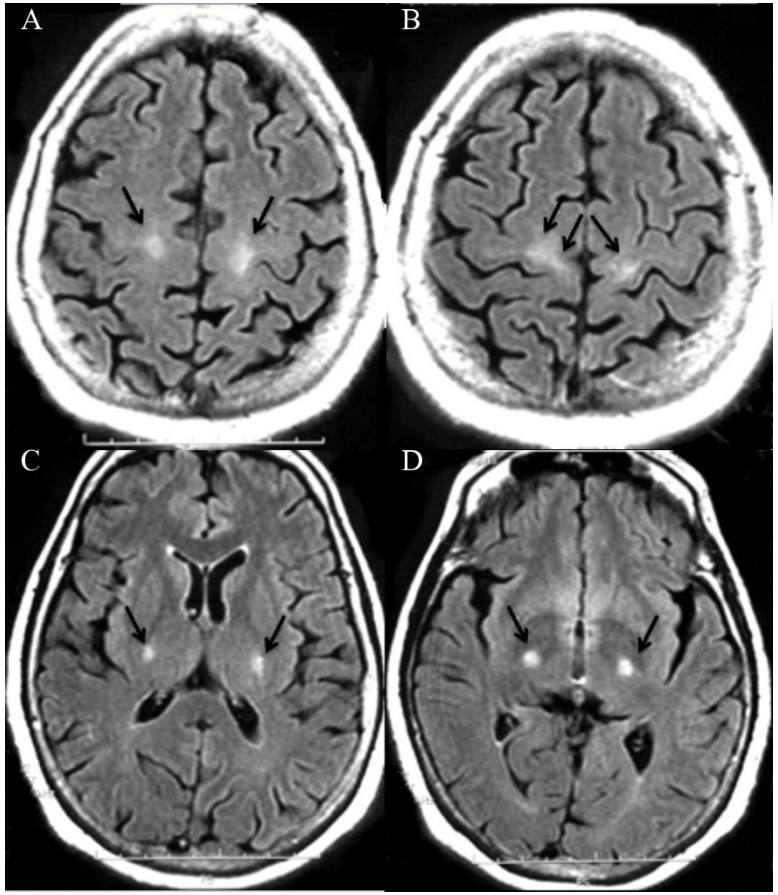
Methods: Forty-five patients with CUP underwent baseline clinical evaluation and MRI with calculation of MRPI. All patients were divided in 2 groups according to MRPI values. A group included 30 patients with CUP with normal MRPI values while the other group included 15 patients with CUP with MRPI values suggestive of PSP (higher than 13.55). A clinical follow-up was performed in all patients.

Results: Duration of clinical follow-up in these 2 groups was 28.4 ± 11.7 months (mean ± SD). None of the patients with CUP with normal MRPI values fulfilled established clinical criteria for PSP (follow-up ranging from 24 to 60 months). By contrast, 11 of 15 patients with CUP with abnormal MRPI values (higher than 13.55) developed during the follow-up (range from 6 to 48 months) additional clinical features characteristic of probable (1 patient) or possible (10 patients) PSP. MRPI showed a higher accuracy in predicting PSP (92.9%) than clinical features, such as vertical ocular slowness or first-year falls (61.9% and 73.8%, respectively).

Conclusions: Our findings suggest that MRPI is more powerful than clinical features in predicting the evolution of CUP toward PSP phenotypes. *Neurology*® 2011;77:1042–1047

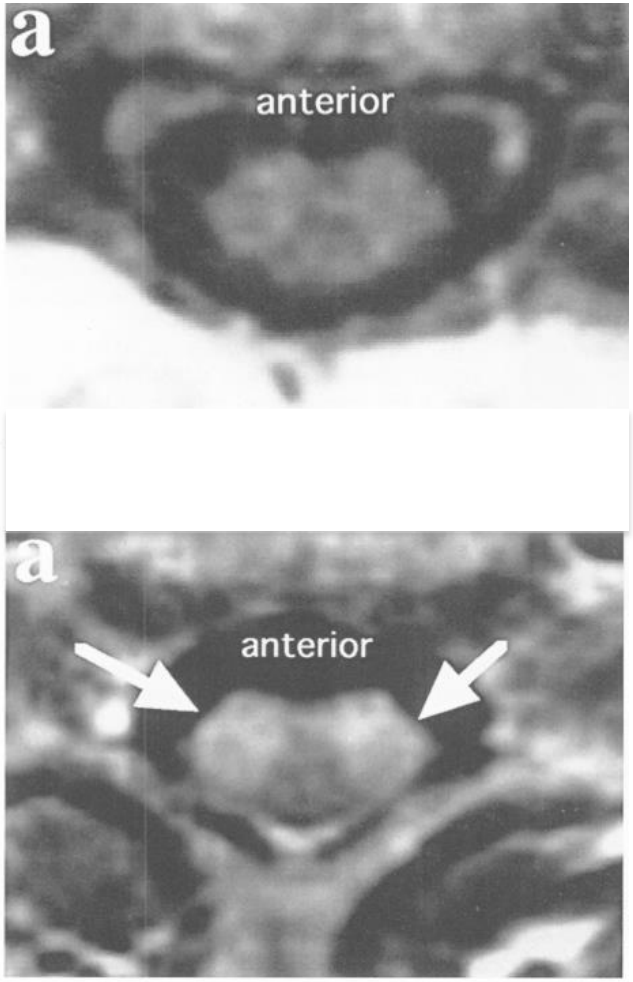
Motor neuron disorders

- T2-hyperintensity of the corticospinal tract can be pronounced in ALS but has low sensitivity (about 40%) and limited specificity (about 70%)



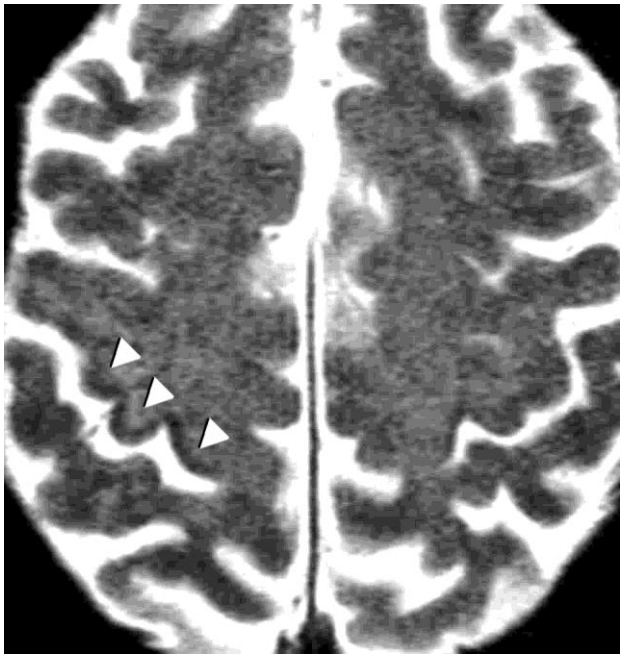
Motor neuron disorders

- T1 hyperintensity ALC



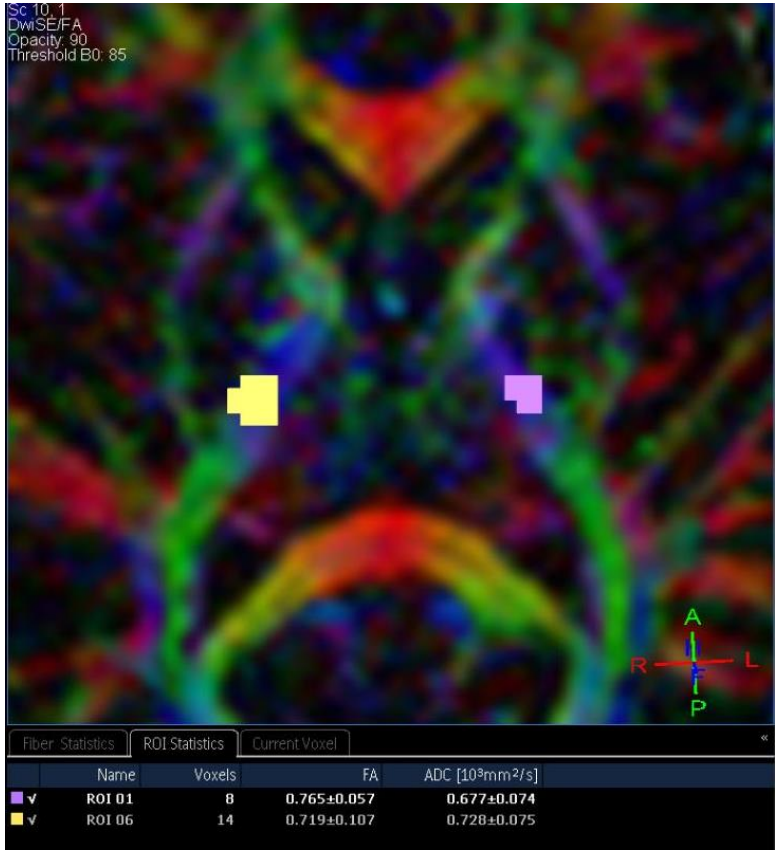
Masaaki Waragai, 1997

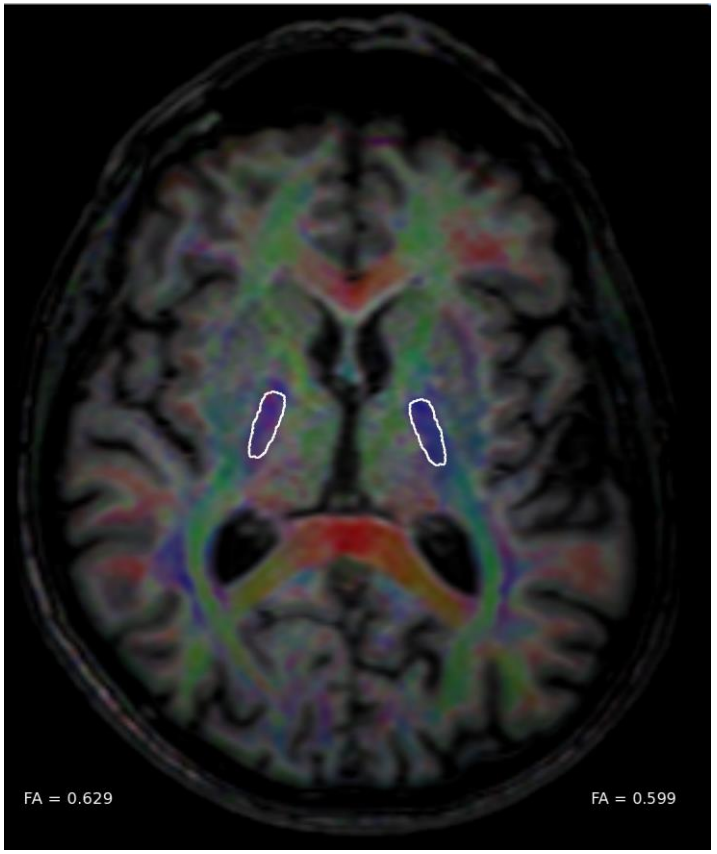
- T2 hypointensity MC



Motor neuron disorders

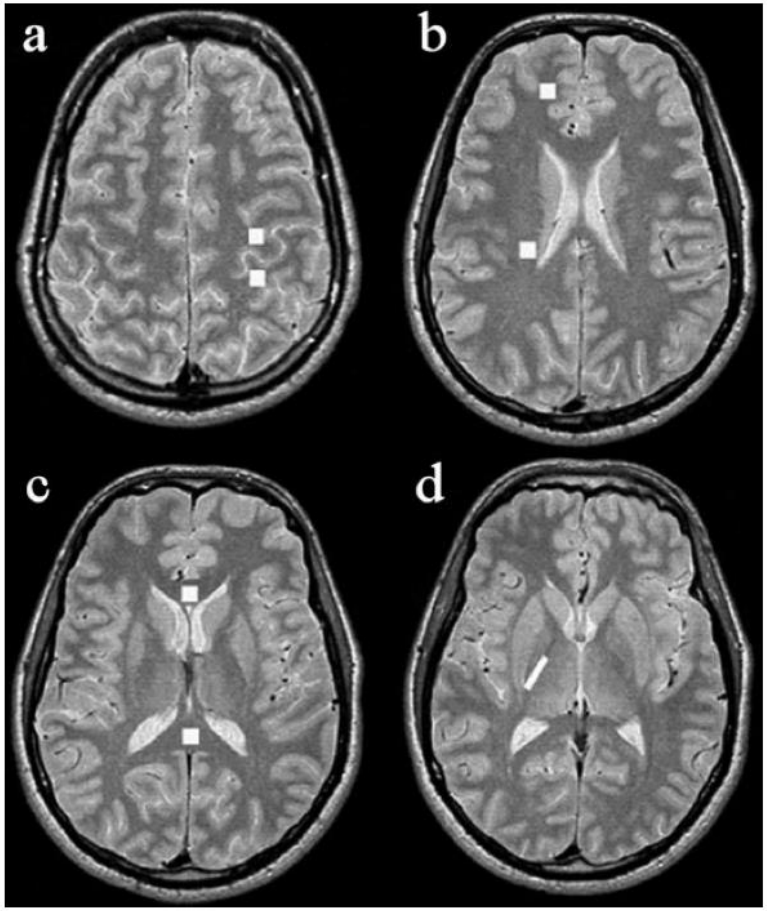
- Change in FA might be an early indicator of ALS, with MD changes being more chronic and indicative of neuronal loss.





Motor neuron disorders

- Does a FA cut-off exist for ALS?



J.M. Graham. Neurology 2004

An upper threshold FA value in the posterior limb of the internal capsule of 0.72 had a sensitivity of 95%, a specificity of 71%, and a positive predictive value of 82%

Conclusions

- BOLD imaging delivered important insights into neurodegenerative disease knowledge
- However, practical use in single subjects is still far away
- Which Biomarkers class will be most suited for fMRI:

  A-diagnostic / B-monitoring ?
- AD the closest to clinical application
- «Competition» with PET, CSF and Morphometry → Multimodal?