ASSOCIAZIONE ITALIANA PSICOGERIATRIA

8° CONVEGNO su:

COGNITIVITÀ E MALATTIE NEUROLOGICHE

Torino, 8 Novembre 2019

EDUCATORIO DELLA PROVVIDENZA - SALA ORPHEUS

Corso Trento, 13 - 10129 Torino

ASL CITTÀ DI TORINO

NEUROIMAGING

Daniela Perani

San Raffaele University

Nuclear Medicine Unit San Raffaele Hospital

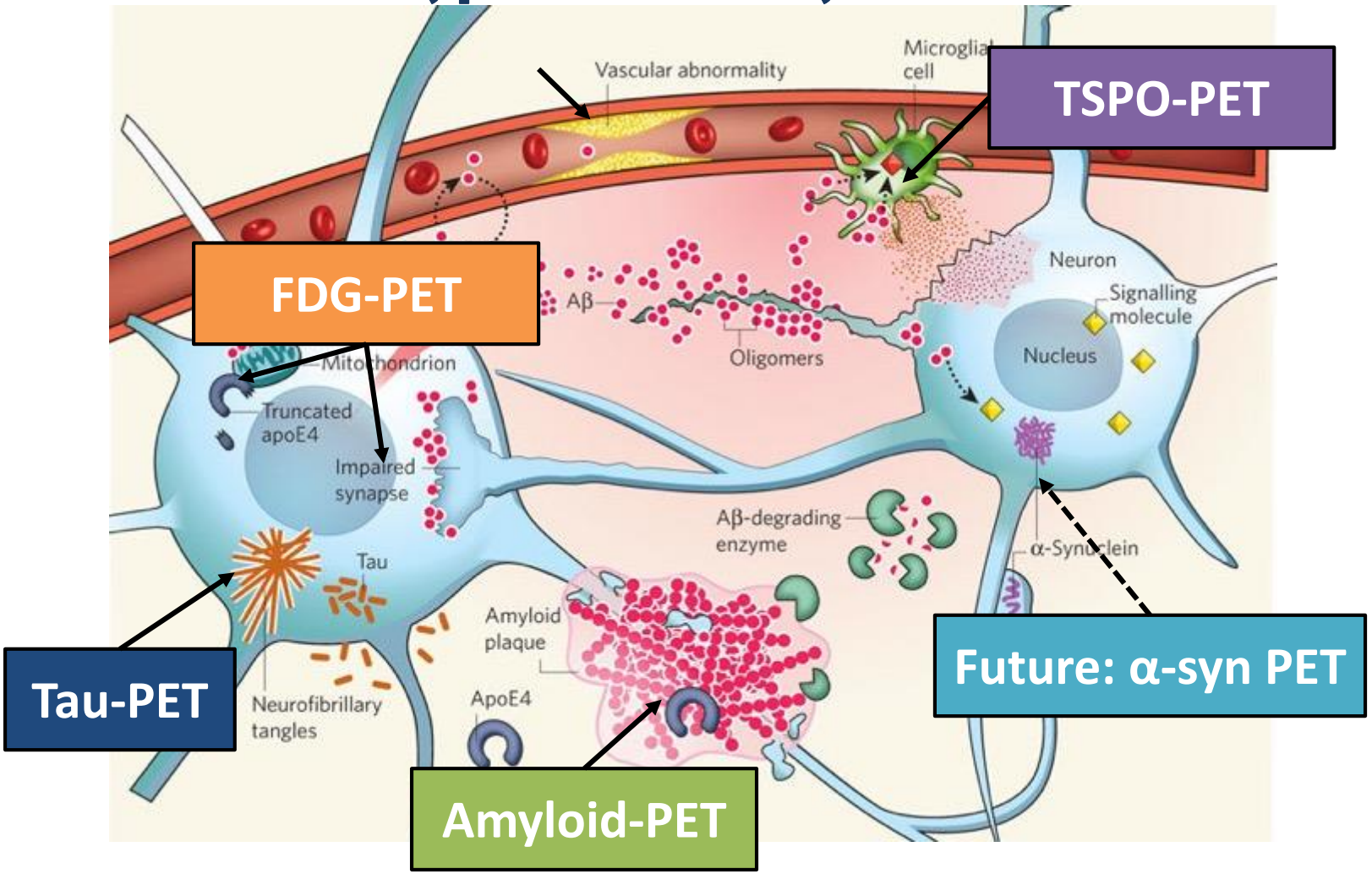
Division of Neuroscience IRCCS San Raffaele

Milano

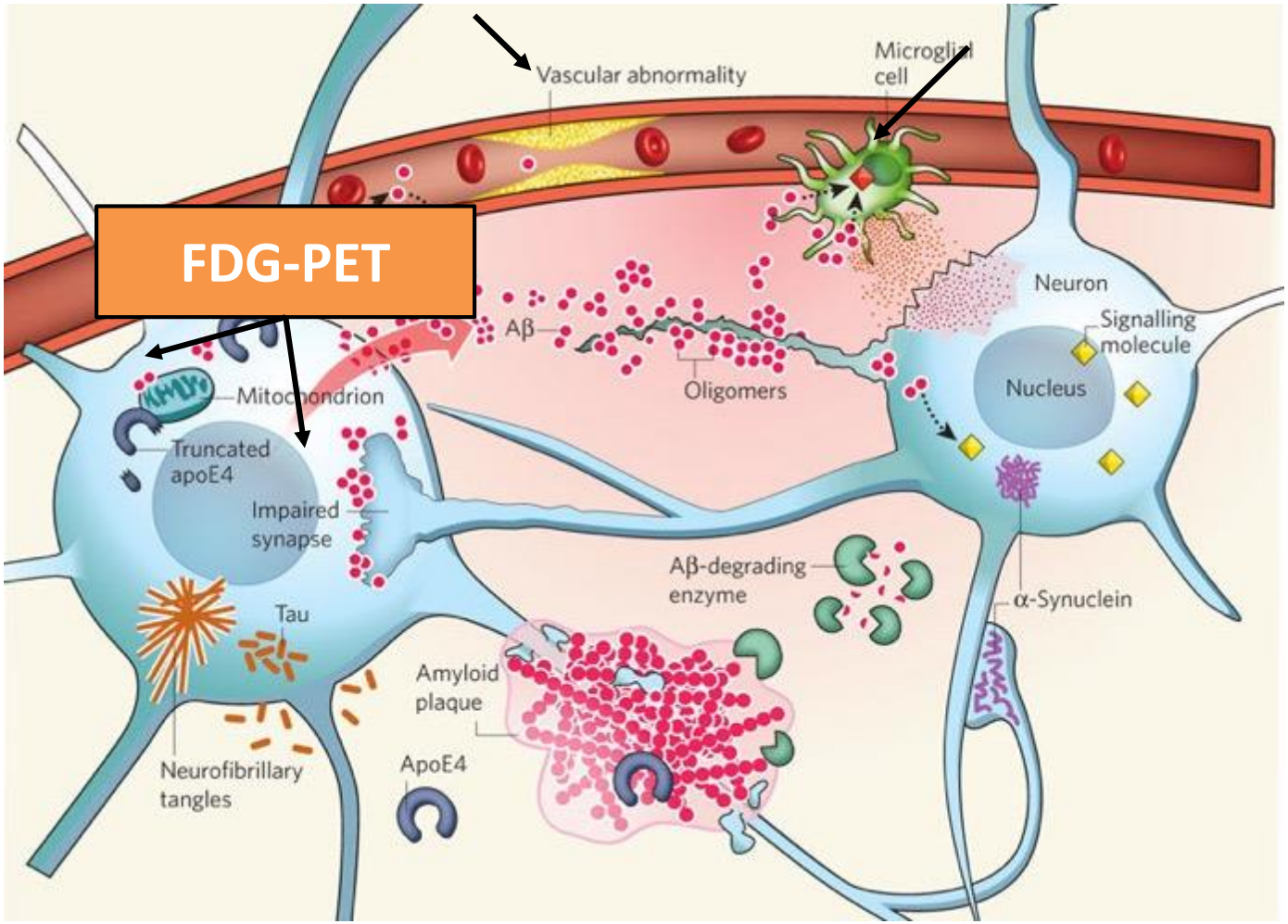
Torino, 23 ottobre 2015

PET-CT and PET-MRI

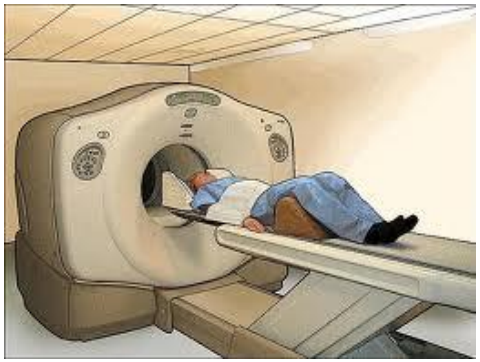
PET in NEURODEGENERATIVE DISEASES:
glucose metabolism, protein burden, neuroinflammation

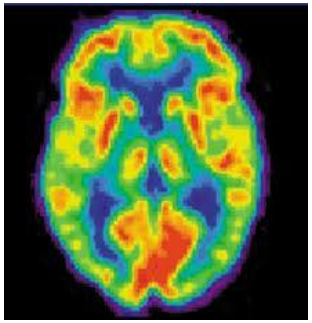


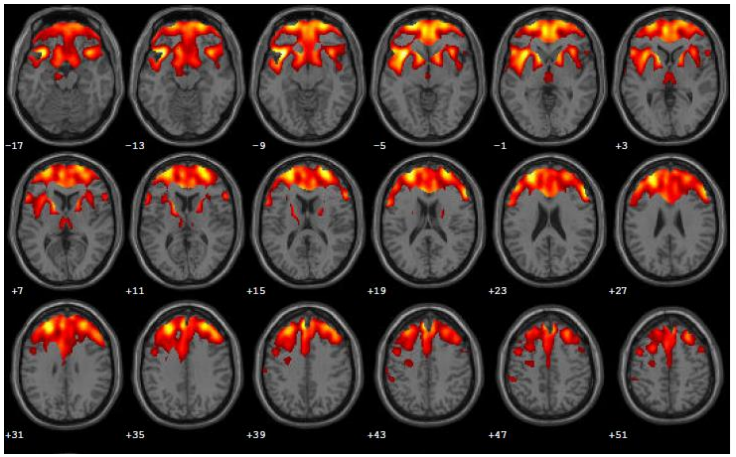
PET in ND: glucose metabolism, protein accumulation, neuroinflammation



Role of PET imaging in clinical settings





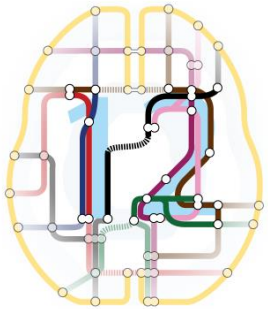


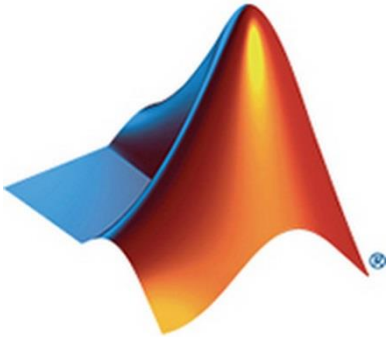
More than 20 years of research in FDG PET molecular imaging

provided *specific metabolic patterns* for the different neurodegenerative disorders

The importance of quantification

absolute or parametric measures

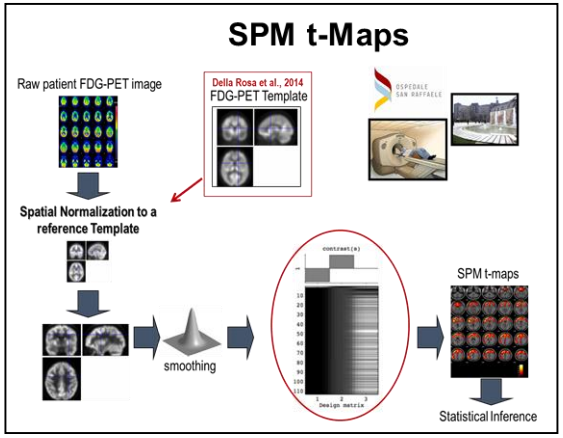


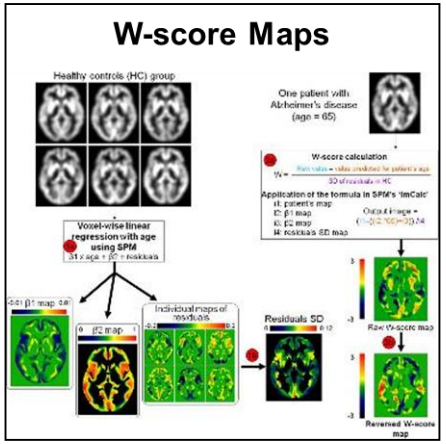


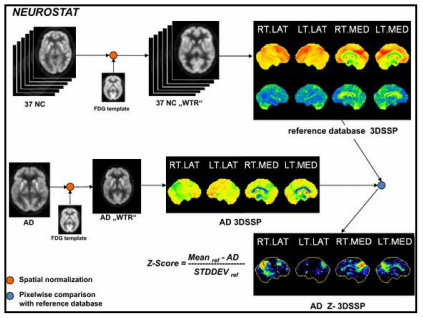
VOXEL-BASED SEMI-QUANTITATIVE ANALYSIS

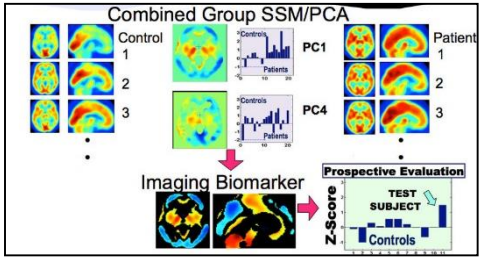
Tools:

- ***NeuroQ (Syntermed)***
- ***NeuroClick (Hermes)***
- ***PMOD software***
- ***SPM***
- **W-score Maps**
- ***Multivariate analysis***







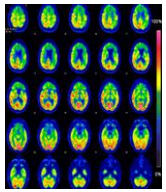


Common denominator is a <u>normal database</u>

<u>Greater sample sizes in normal database provide more accurate results</u>

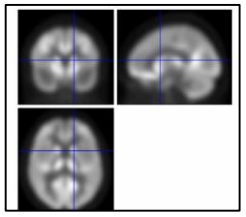
OPTIMIZED FDG PET SPM PROCEDURE

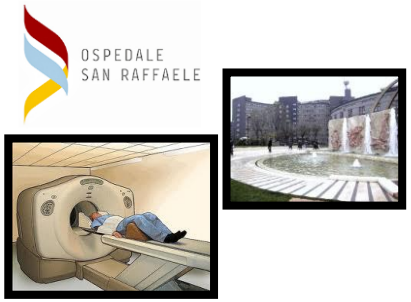
Raw patient FDG PET image



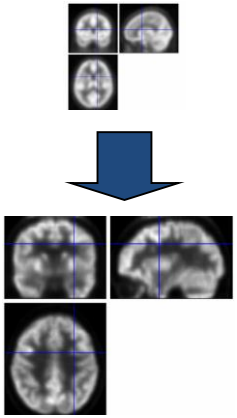
Della Rosa et al., 2014

FDG PET Template

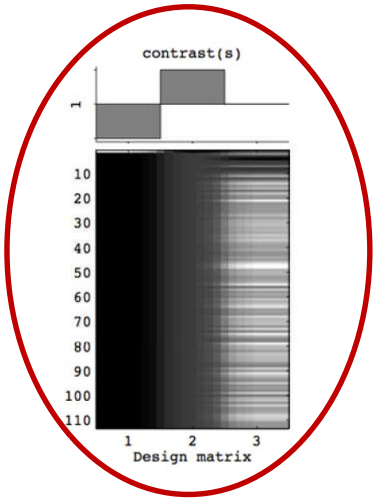




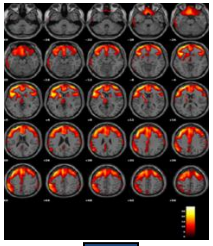
Spatial Normalization to
a reference Template



smoothing



SPM t-maps



Statistical Inference

Perani et al., Neuroimage Clin, 2014; Della Rosa et al., Neuroinformatics, 2014

THE NEED FOR METRICS

Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 785039, 22 pages
http://dx.doi.org/10.1155/2014/785039

Hindawi

Review Article

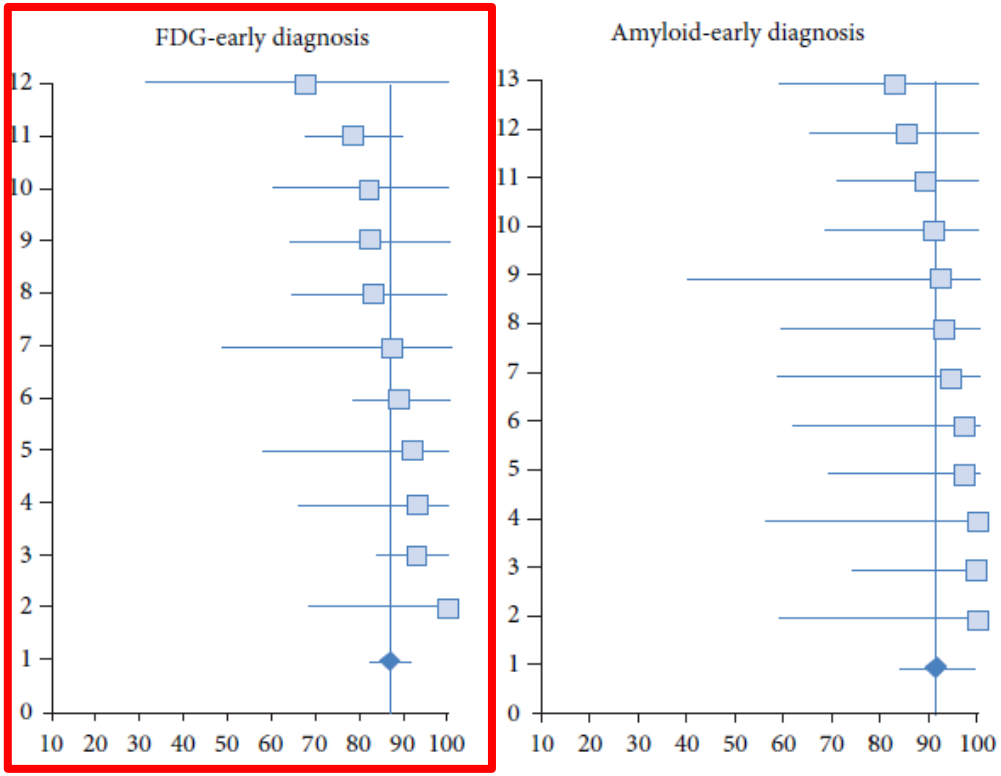
A Survey of FDG- and Amyloid-PET Imaging in Dementia and GRADE Analysis

**Perani Daniela,[1] Schillaci Orazio,[2] Padovani Alessandro,[3]
Nobili Flavio Mariano,[4] Iaccarino Leonardo,[1] Della Rosa Pasquale Anthon
Frisoni Giovanni,[6] and Caltagirone Carlo[7]**

Meta-Analysis and GRADE Analysis.

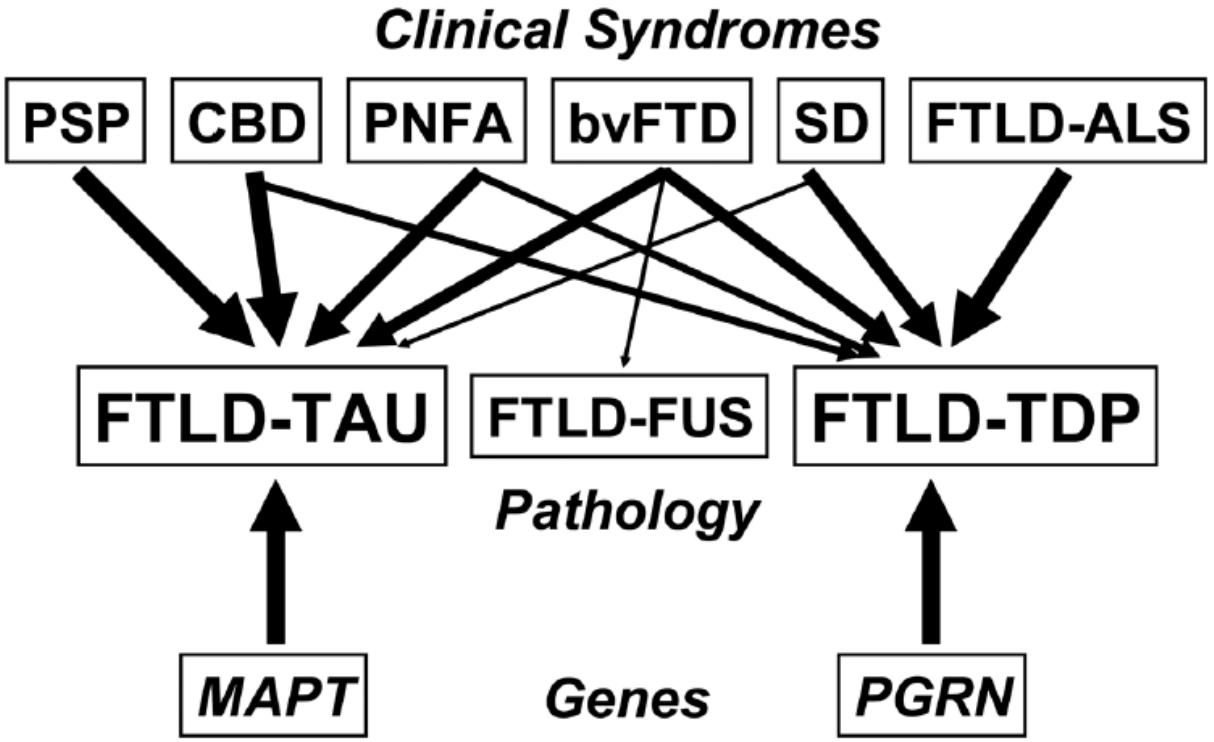
sensitivity :

0.86 for Early Diagnosis (MCI)
0.90 for Differential Diagnosis

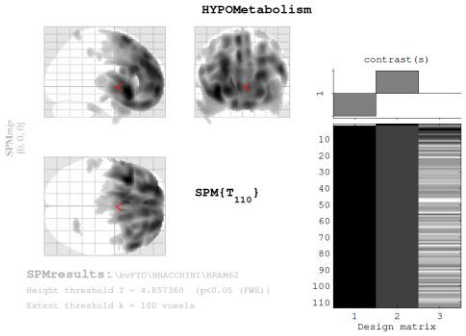


Perani et al. Biomed Res Int, 2014

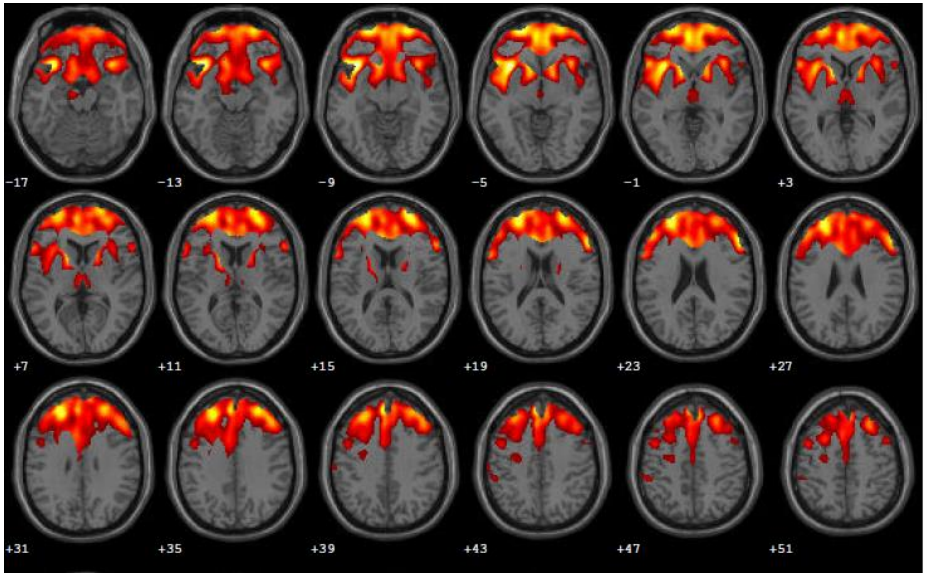
FRONTOTEMPORAL LOBAR DEGENERATION SPECTRUM



FDG PET SPM MAPS in BEHAVIORAL VARIANT FTD SINGLE SUBJECT



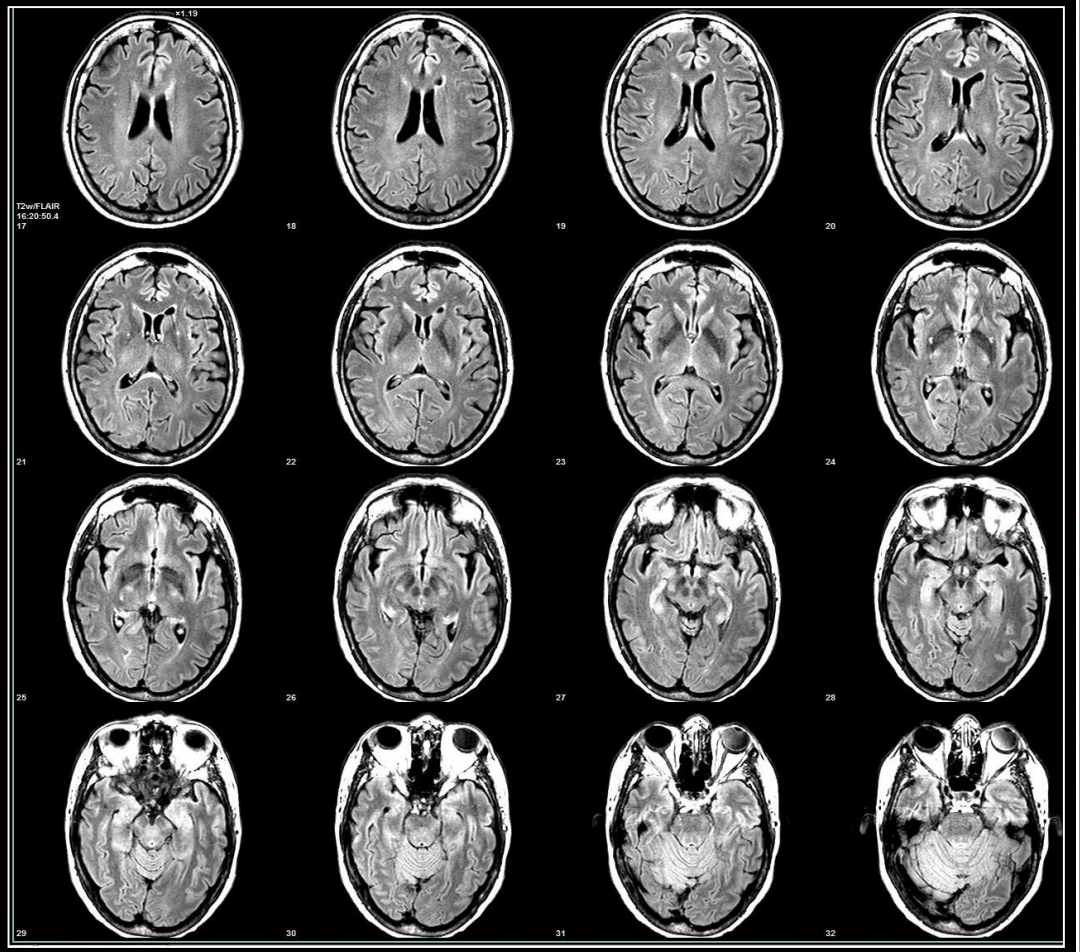
VOXEL-BASED SPM ANALYSIS



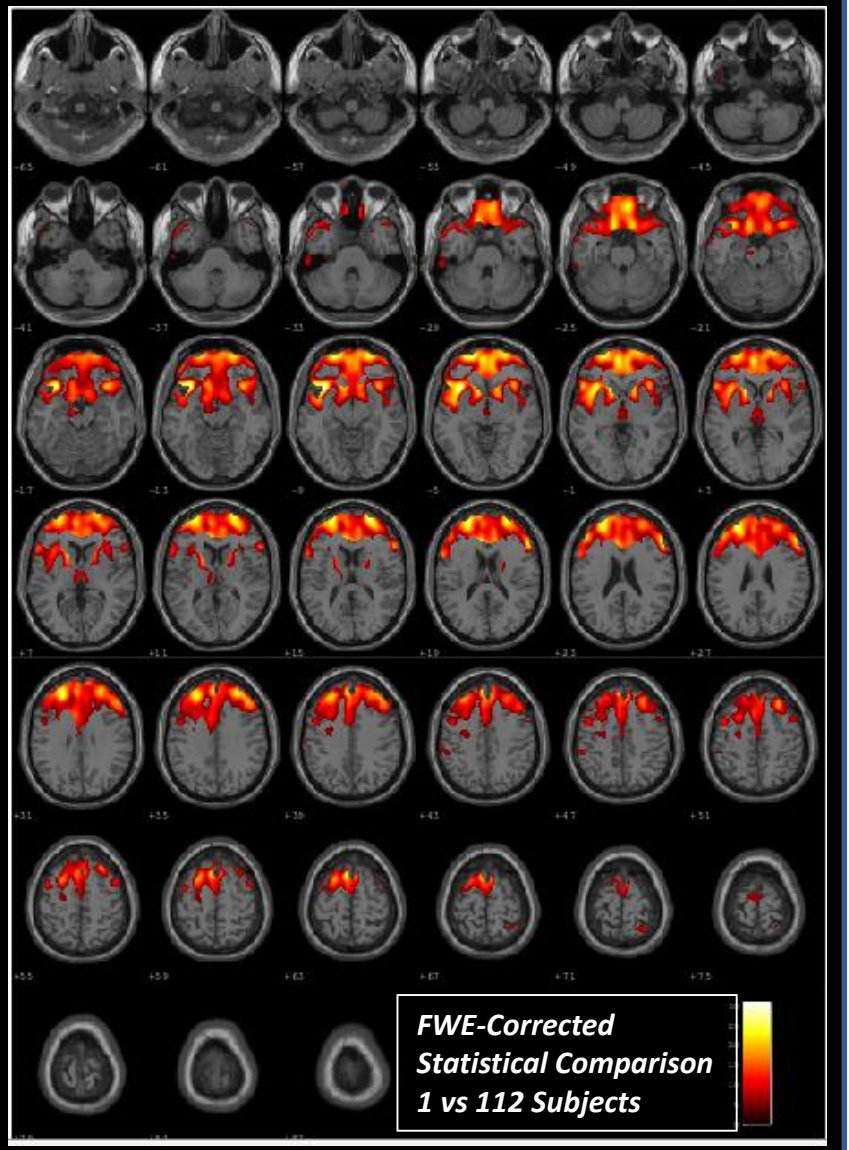
Cerami et al. Cortex, 2016

bvFTD 59 years old

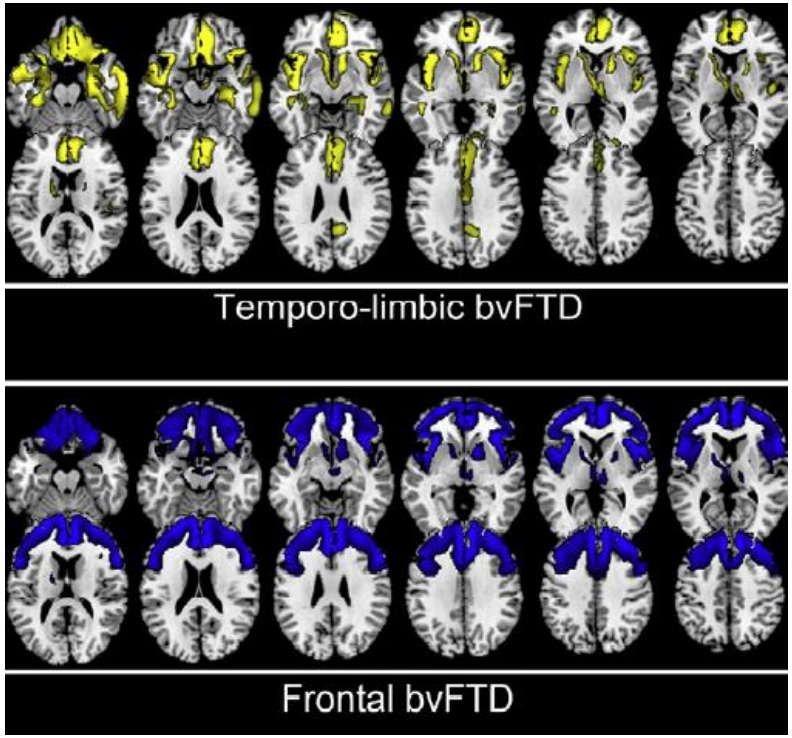
MRI T2 Flair



FDG-PET SPM Map

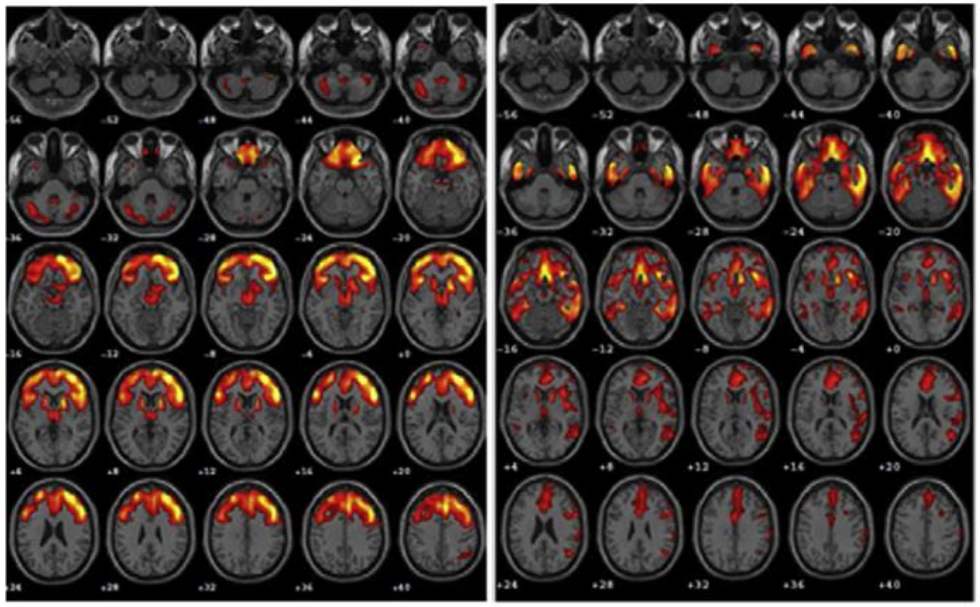


BEHAVIORAL VARIANTS OF FTD SINGLE SUBJECT



VOXEL-BASED SPM ANALYSIS

FRONTAL PATTERN **TEMPORO-LIMBIC PATTERN**



Cerami et al., Cortex 2016

Neuropsychological profiles

	FRONTAL	TEMPOROLIMBIC	Statistics
Number of subjects	25	27	-
Gender *(female/male)*	11/14	12/15	n.s.
Age in years *(mean/st.dev.)*	65.96±7.50	72.9±7.083	F<TL *
Education *(mean/st.dev.)*	11.12±4.51	10.78±4.61	n.s.
CDR sum of boxes *(mean/st.dev.)*	4.84±2.06	5.48±3.57	n.s.
Disease duration *(mean/st.dev.)*	26.8±13.54	34.81±27.15	n.s.
MMSE raw score *(mean/st.dev.)*	22.04±5.76	22.67±5.74	n.s.
Presenting symptoms *(n. of cases)*	Behavior n=16 Behavior + Language n=8 Language n=1	Behavior n=11 Behavior + Memory n=9 Memory n=6 Prosopagnosia n=1	-
Family history of neuropsychiatric conditions *(n. of cases)*	21	22	n.s.
Bipolar syndrome or depression in anamnesis *(n. of cases)*	4	4	n.s.
Behavioral disinhibition *(n. of cases)*	1	2	F≠TL ∫ *
Apathy or inertia *(n. of cases)*	10	6	
Both disinhibition and apathy *(n. of cases)*	14	19	
Loss of empathy or sympathy *(n. of cases)*	18	19	n.s.
Perseverative, stereotyped, or compulsive/ritualistic behaviors *(n. of cases)*	14	20	n.s.
Hyperorality and dietary changes *(n. of cases)*	8	9	n.s.
Executive deficits *(n. of cases)*	24	16	F≠TL ₱ *
Immediate recall memory impairments *(n. of cases)*	0	0	
Delayed recall memory impairments *(n. of cases)*	1	5	F≠TL § *
Both immediate and delayed recall memory impairments *(n. of cases)*	14	7	
No immediate and delayed recall memory impairments *(n. of cases)*	8	6	

Cerami et al., Cortex 2016

RESEARCH DIAGNOSTIC CRITERIA including FDG PET

LEWY BODY DISEASE

- McKeith, I.G., Boeve BF, Dickson, D.W et al., **2017**.Diagnosis and management of **dementia with Lewy bodies**: Fourth Consensus report of the DLB Consortium. Neurology 89:1–13

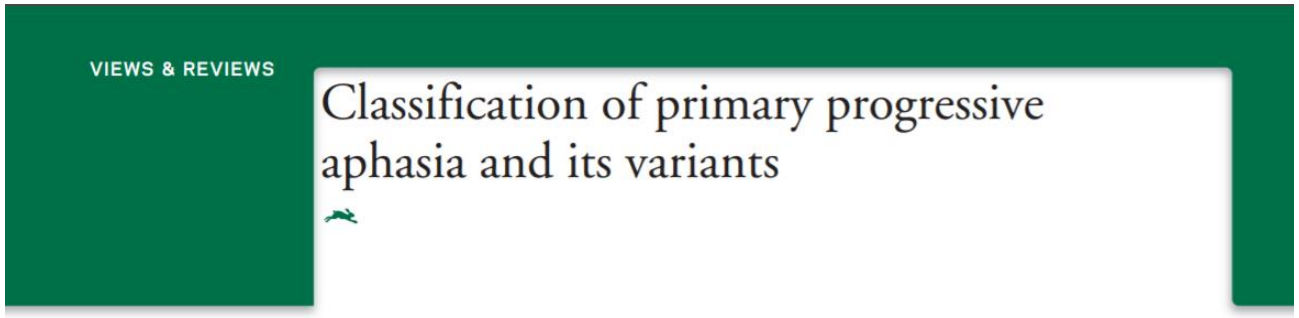
FRONTOTEMPORAL DEGENERATION SPECTRUM

- Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., et al., **2011**. Sensitivity of revised diagnostic criteria for the **behavioural variant of Frontotemporal dementia.** Brain 134 (9), 2456–2477

- Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., et al.,**2011**. Classification of **primary progressive aphasia and its variants**. Neurology 76 (11), 1006–1014

- Armstrong, M.J., Litvan, I., Lang, A.E., Bak, T.H., Bhatia, K.P., Borroni, B., et al., **2013**. Criteria for the diagnosis of **corticobasal degeneration**. Neurology 80 (5), 496–503

PRIMARY PROGRESSIVE APHASIAs

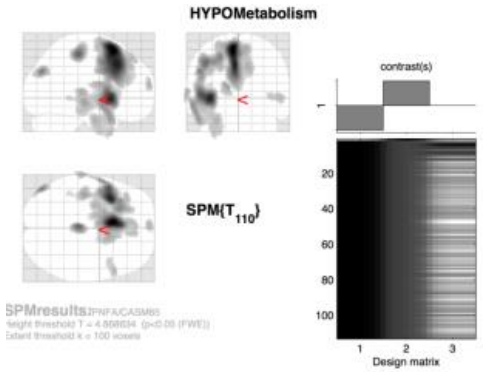


Heterogeneous clinical phenotypes are associated with the PPA (nf-PPA, sem-PPA, lv-PPA) , and recent review studies refer to Alzheimer disease (AD), corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP)

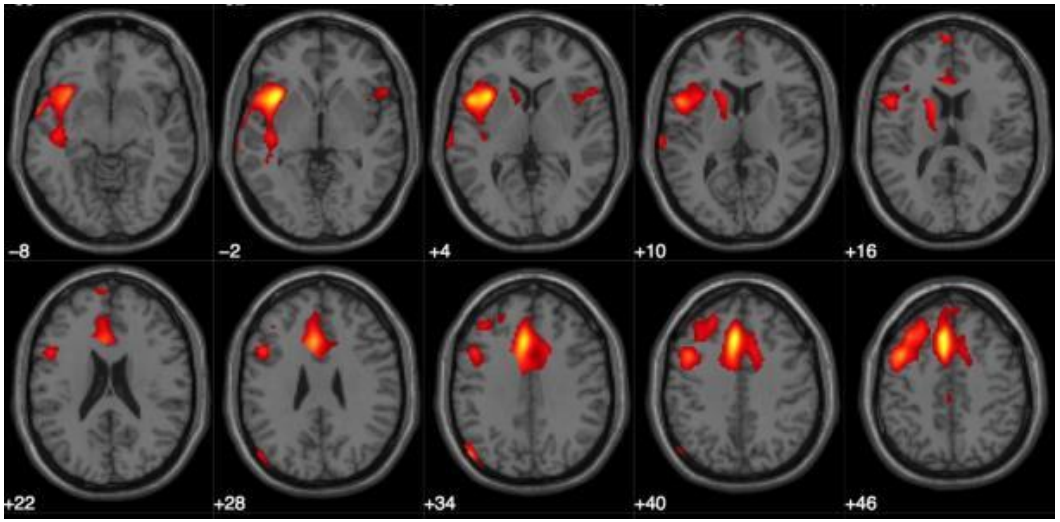
The topography of FDG PET brain hypometabolism represents the major signature of the clinical PPA phenotype

Gorno-Tempini et al., Neurology 2011

NON-FLUENT PROGRESSIVE APHASIA VARIANT SINGLE SUBJECT



VOXEL-BASED SPM ANALYSIS



Cerami et al., JAD 2016

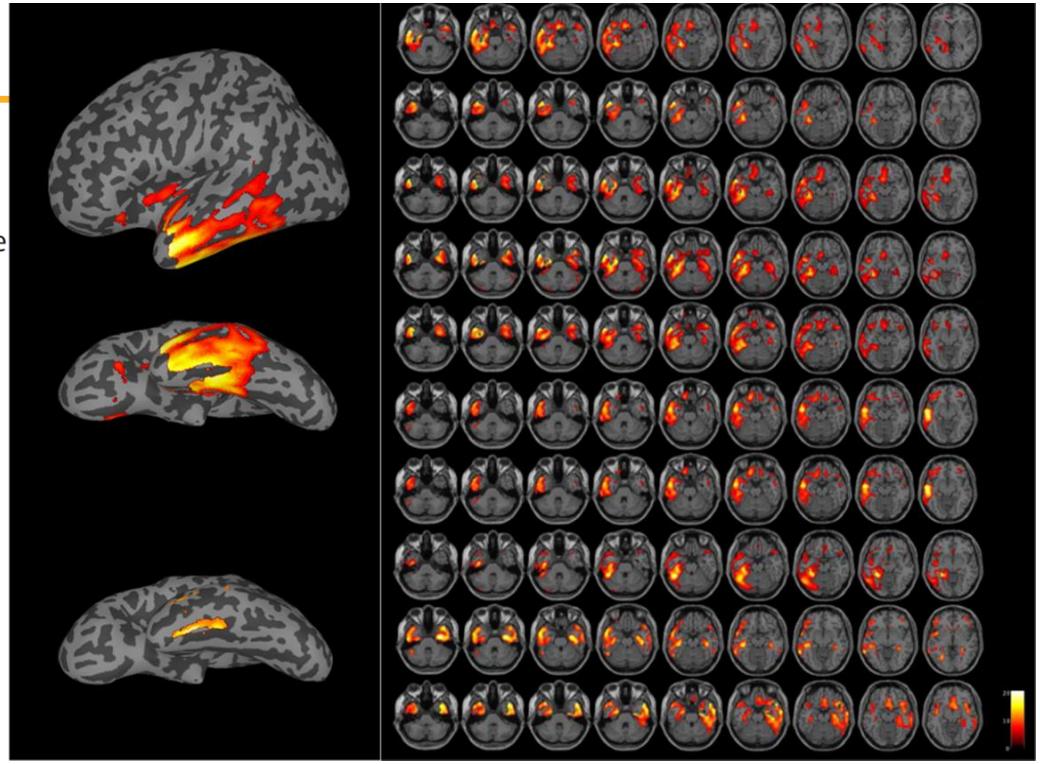
SEMANTIC PPA VARIANT OF FTD SINGLE SUBJECT

PLOS ONE

RESEARCH ARTICLE

The Semantic Variant of Primary Progressive Aphasia: Clinical and Neuroimaging Evidence in Single Subjects

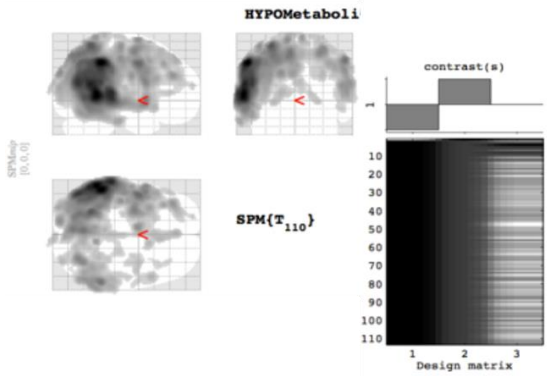
Leonardo Iaccarino[1], Chiara Crespi[1,2], Pasquale Anthony Della Rosa[3], Eleonora Catricalà[4], Lucia Guidi[4], Alessandra Marcone[5], Fabrizio Tagliavini[6], Giuseppe Magnani[7], Stefano F. Cappa[4,2], Daniela Perani[1,2,3,8]*



Iaccarino et al., PLOS ONE 2015

Cerami et al., JAD 2016

LOGOPENIC aphasia AD VARIANT SINGLE SUBJECT



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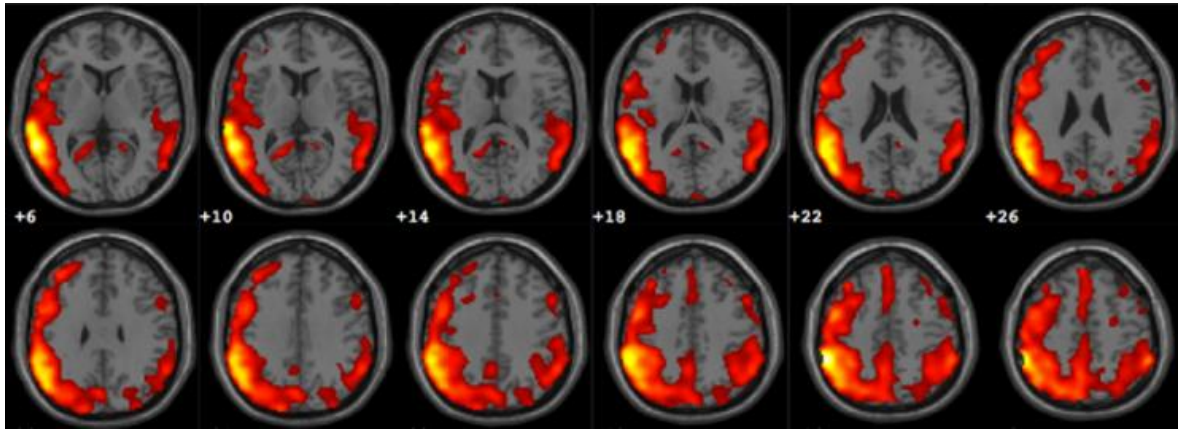

Cerami et al. JAD, 2016

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- Armstrong, M.J., Litvan, I., Lang, A.E., Bak, T.H., Bhatia, K.P., Borroni, B., et al., **2013**. Criteria for the diagnosis of **corticobasal degeneration**. Neurology 80 (5), 496–503

PARKINSONIAN SYNDROMES

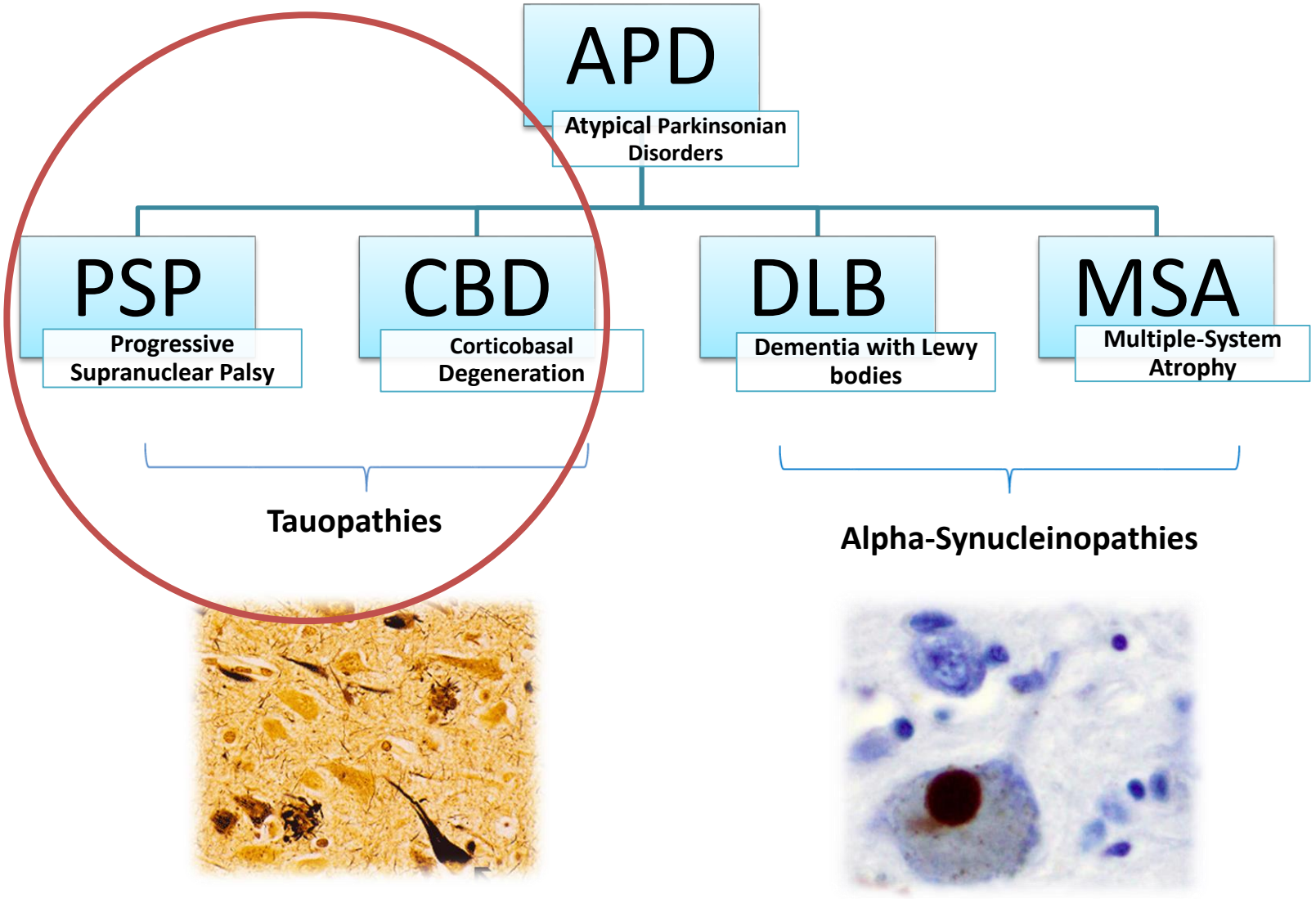
The Parkinsonian Disorders (APD) frequently overlap in clinical presentations, making the differential diagnosis challenging, particularly in the early stages

Low dopamine transporter uptake at SPECT is present in all the parkinsonian syndromes making its role in the differential diagnosis of APD not possible

The dysfunctional brain patterns revealed by FDG PET represent biomarkers of local synaptic dysfunction associated with disease-specific alterations characterizing APD conditions

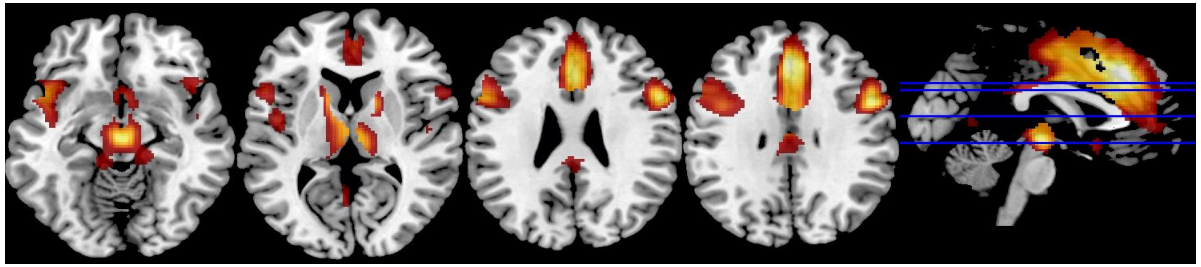
McKeith et al. Neurology 2017; Gilman et al. Neurology 2008; Armstrong et al Neurology 2013

Atypical Parkinsonisms: a cluster of biologically and clinically different entities

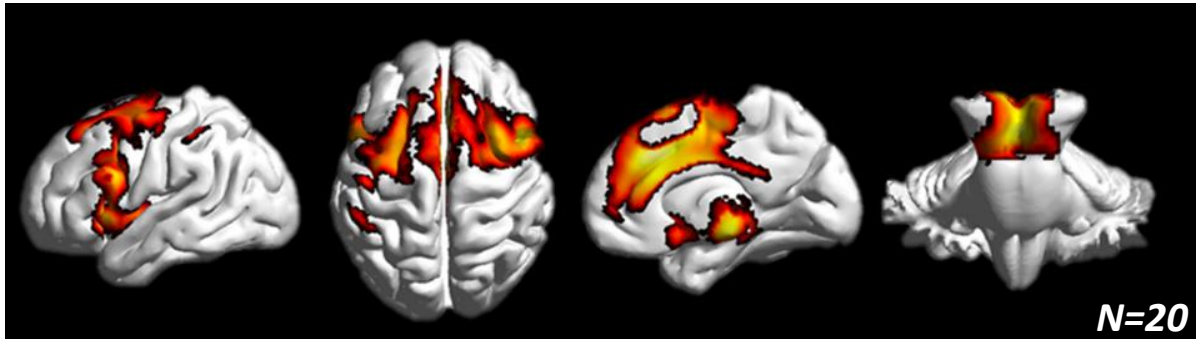


Progressive supranuclear palsy

[^{18}F]FDG-PET SPM Single-subject Analysis



[^{18}F]FDG-PET SPM Commonality Analysis



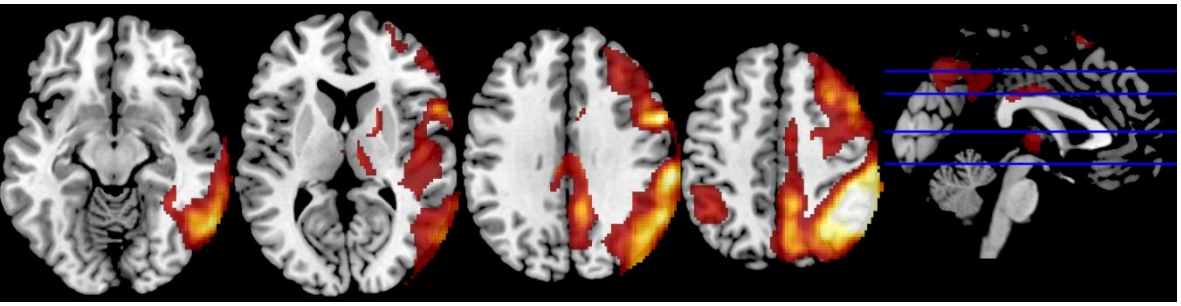
Metabolic reductions in:

- **Upper brainstem**
- **Thalami**
- **Caudate**
- **Frontal opercula**
- **Middle frontal cortex**
- **Anterior cingulate gyrus**

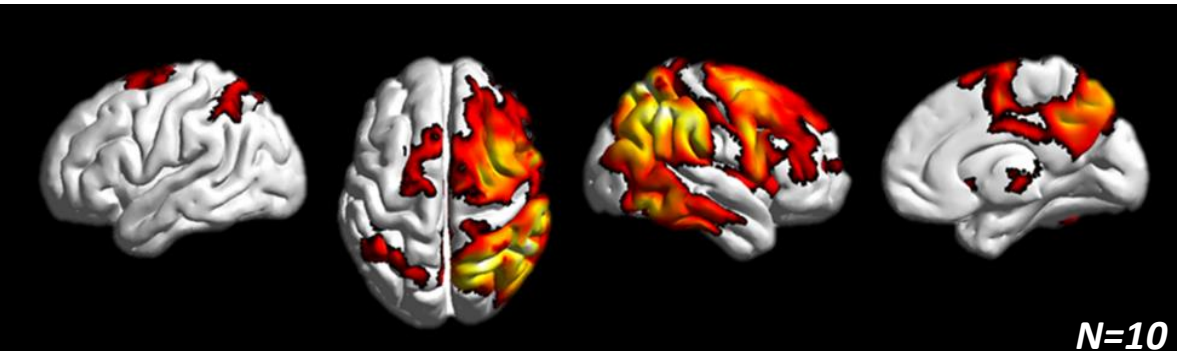
Caminiti et al., EJN 2017

Corticobasal degeneration (CBD)

[^{18}F]FDG-PET SPM Single-subject Analysis



[^{18}F]FDG-PET SPM Commonality Analysis

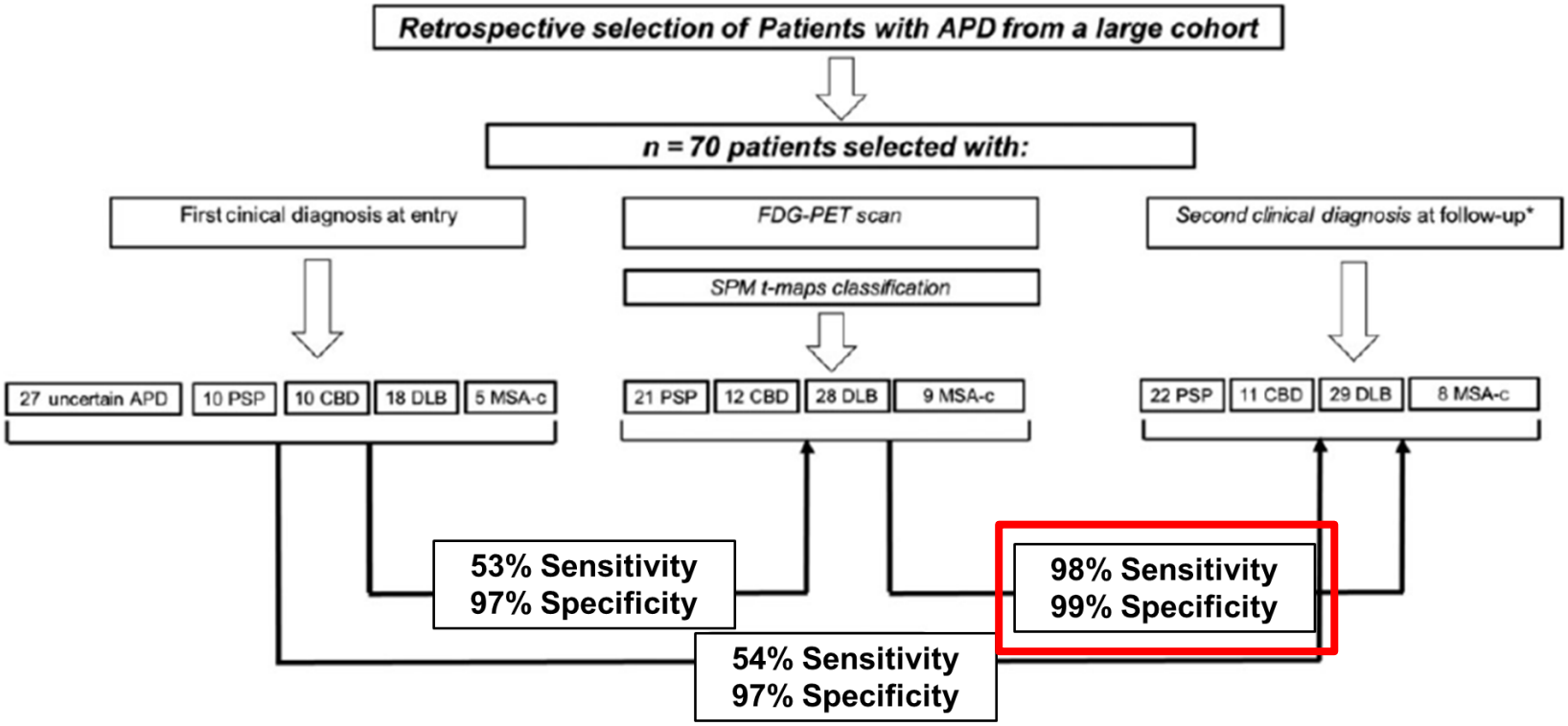


***Asymmetric reductions in*:**

- **Thalamus**
- **Striatum**
- **Precentral gyrus**
- **Frontoparietal areas**
- **Middle cingulate gyrus**

Caminiti et al., EJN 2017

FDG PET ACCURACY



FDG PET SPM showed an almost 20% increase in overall accuracy compared to initial clinical classification

Caminiti et al., EJN 2017

RESEARCH DIAGNOSTIC CRITERIA including FDG PET

LEWY BODY DISEASE

- McKeith, I.G., Boeve BF, Dickson, D.W et al., **2017**.Diagnosis and management of **dementia with Lewy bodies**: Fourth Consensus report of the DLB Consortium. Neurology 89:1–13

FRONTOTEMPORAL DEGENERATION SPECTRUM

- Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., et al., **2011**. Sensitivity of revised diagnostic criteria for the **behavioural variant of Frontotemporal dementia.** Brain 134 (9), 2456–2477

- Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., et al.,**2011**. Classification of **primary progressive aphasia and its variants**. Neurology 76 (11), 1006–1014

- Armstrong, M.J., Litvan, I., Lang, A.E., Bak, T.H., Bhatia, K.P., Borroni, B., et al., **2013**. Criteria for the diagnosis of **corticobasal degeneration**. Neurology 80 (5), 496–503

THE CLINICO-METABOLIC CORRELATES OF LANGUAGE IMPAIRMENT IN CBS and PSP

70 patients fulfilling current criteria for probable CBS (n=33) or PSP (n=37)

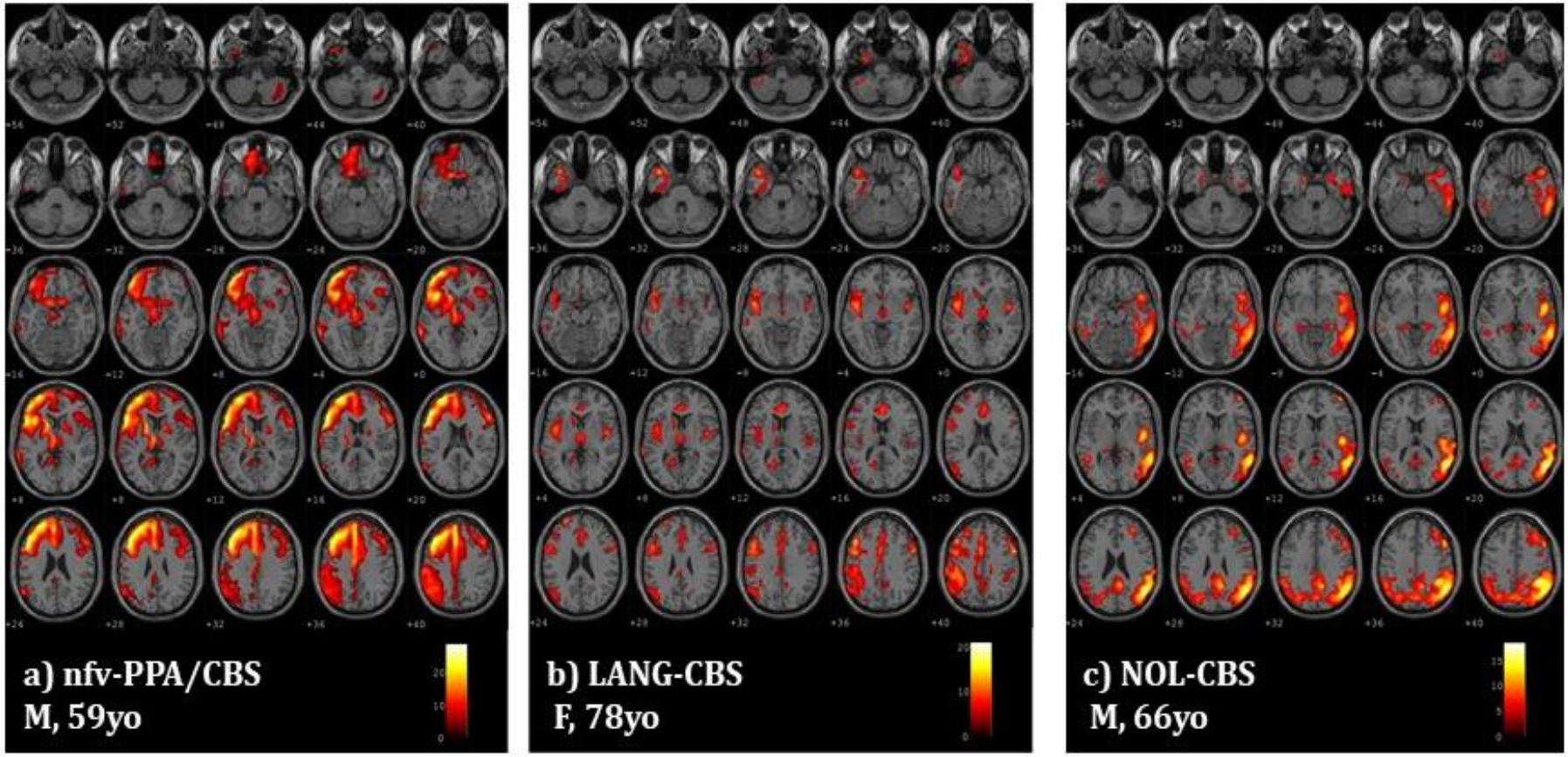
All subjects underwent clinical-neuropsychological and FDG-PET assessments at the time of diagnosis.

The whole patient's cohort was grouped into three subgroups according to the language characteristics:

- **nfv-PPA** *(anomia, agrammatism, impaired comprehension of single words or complex sentences)*
- **subtle language impairments** *not fulfilling nfvPPA criteria*
- **no language deficits**

Dodich et al. NI Clin 2019

SPM maps of significant FDG-PET hypometabolism at the single-subject level in CBS subjects with different language profiles



Dodich et al. NI Clin 2019

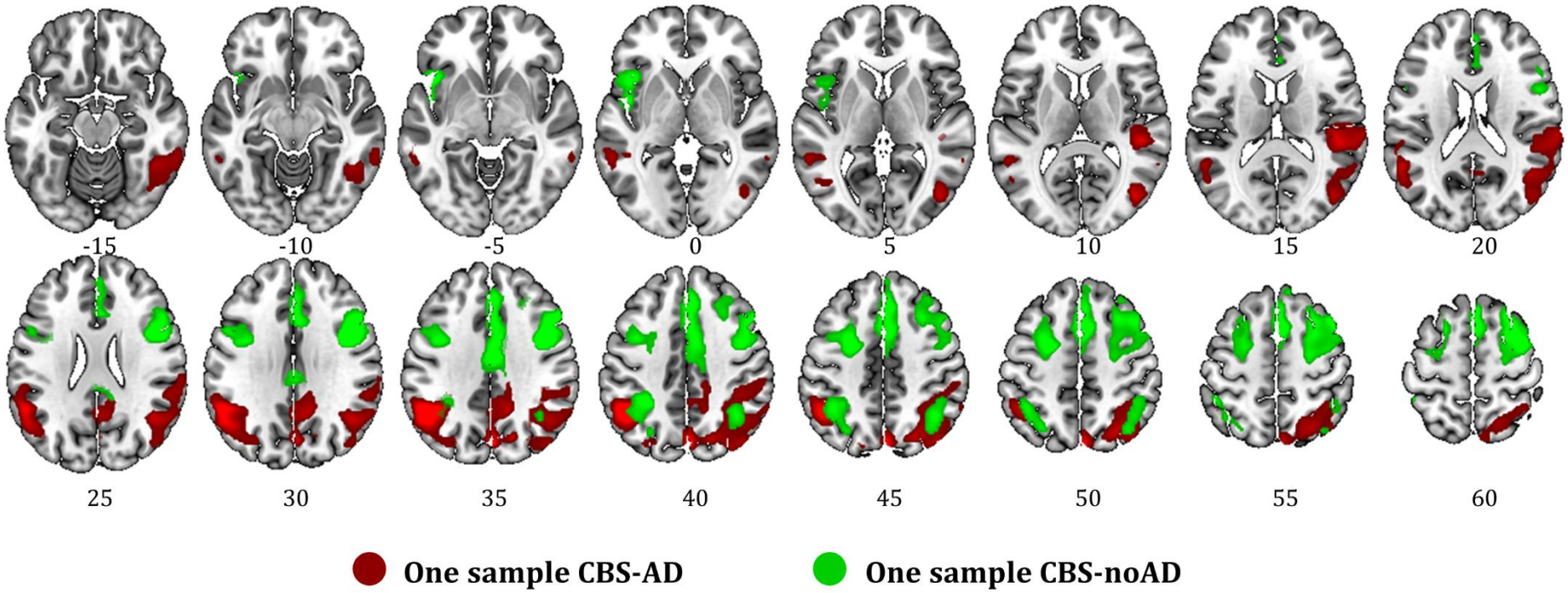
BRAIN METABOLIC SIGNATURES OF CBS DUE TO AD OR NON-AD PATHOLOGY

CBS is the common clinical presentation of patients with CBD pathology

Nevertheless, there are individuals with post-mortem neuropathological changes typical of AD that may show an undistinguished CBS clinical phenotype

Cerami et al. submitted

FDG PET hypometabolism maps



These results suggest the inclusion of FDG-PET imaging in the diagnostic algorithm of individuals with CBS clinical phenotype in order to early identify functional metabolic signatures due to different neuropathological substrates, thus improving the diagnostic accuracy

Cerami et al. submitted

PRE-DEMENTIA PHASE

NeuroImage: Clinical xxx (2018) xxx-xxx

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com

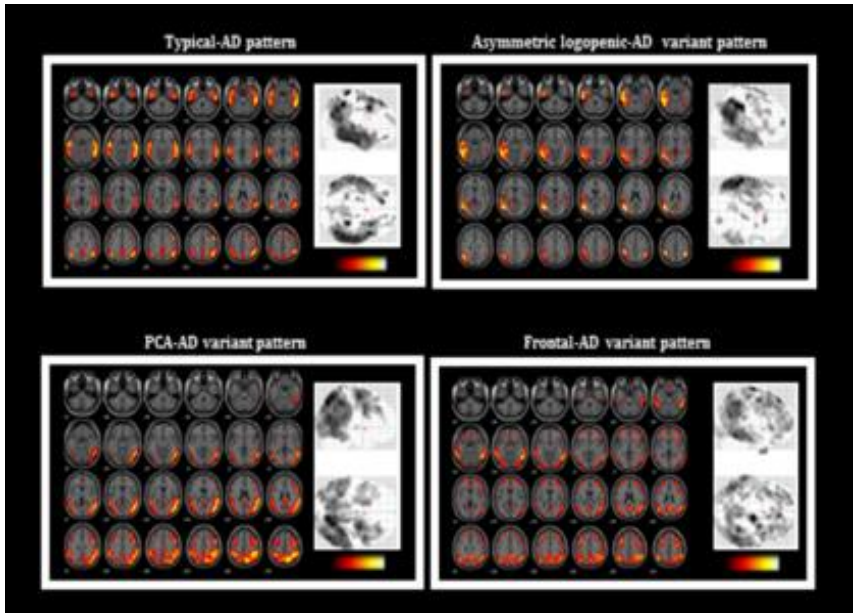
NI Clin 2018

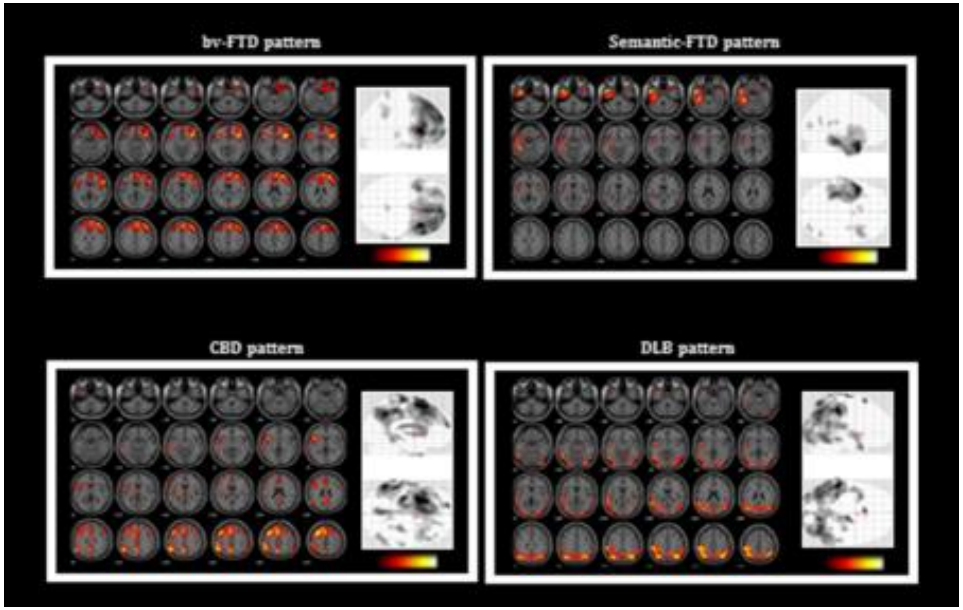
FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicentre MCI cohort

Silvia Paola Caminiti[a, b], Tommaso Ballarini[b], Arianna Sala[a, b], Chiara Cerami[b, c], Luca Presotto[b], Roberto Santangelo[d], Federico Fallanca[e], Emilia Giovanna Vanoli[e], Luigi Gianolli[e], Sandro Iannaccone[c], Giuseppe Magnani[d], Daniela Perani[a, b, e, *], BIOMARKAPD Project

80 MCI

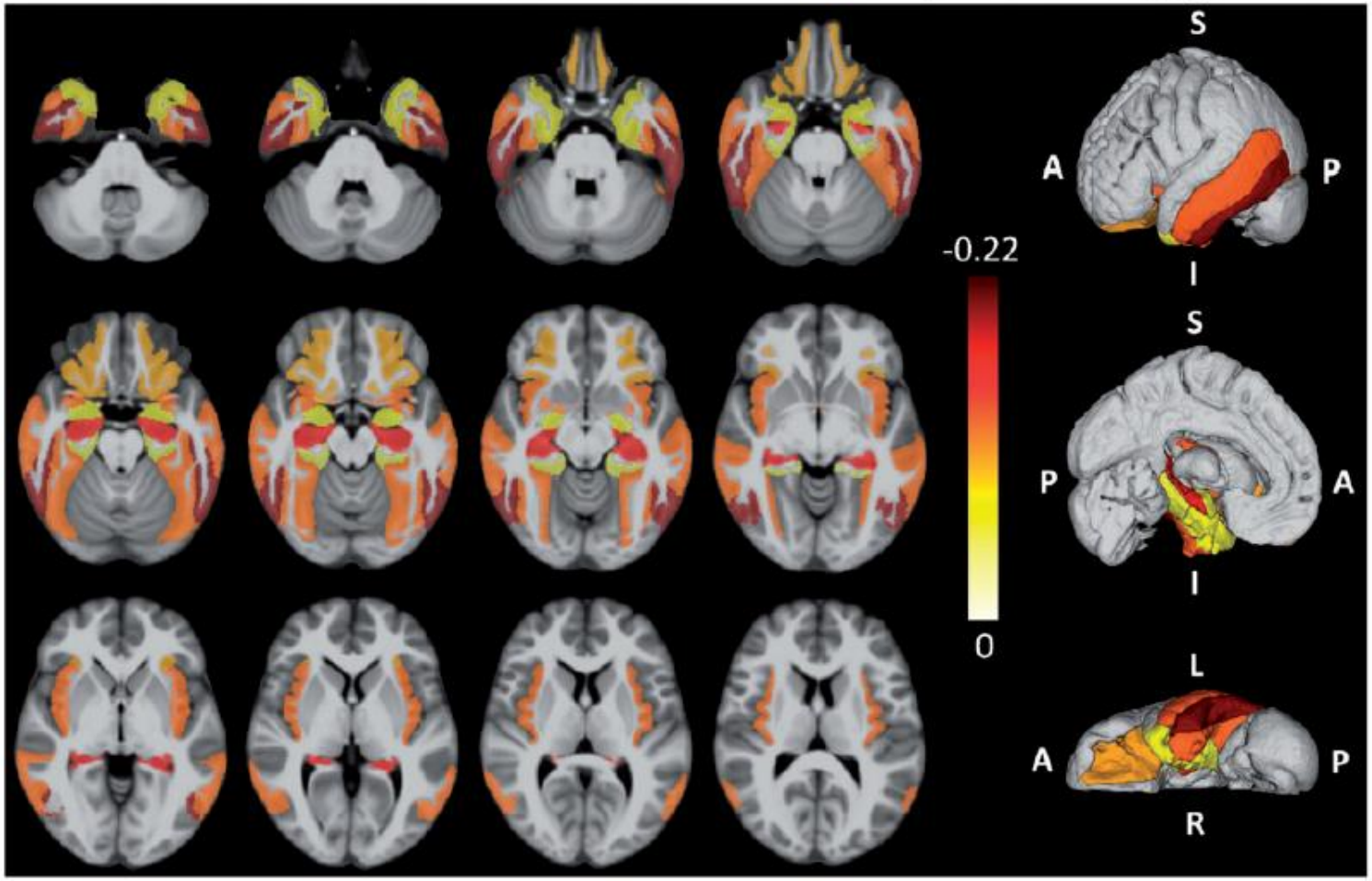
FDG-PET-SPM classification the **most accurate biomarker**, able to provide **disease-specific hypometabolism patterns** in the **prodromal MCI phase**





Biomarkers based definition of limbic predominant long-lasting amnestic Mild Cognitive Impairment

A **Brain atrophy associated with autopsy-confirmed LATE-NC:**
Data from Rush University ROS-MAP community-based autopsy cohorts



Cerami et al. Alzheimer's Research & Therapy (2018) 10:42
https://doi.org/10.1186/s13195-018-0369-8

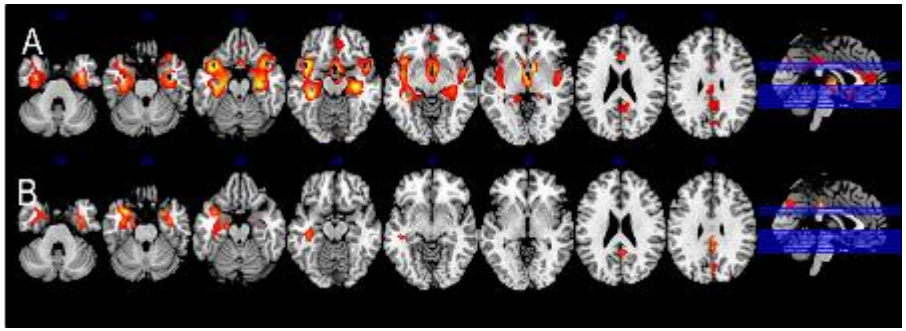
Alzheimer's
Research & Therapy

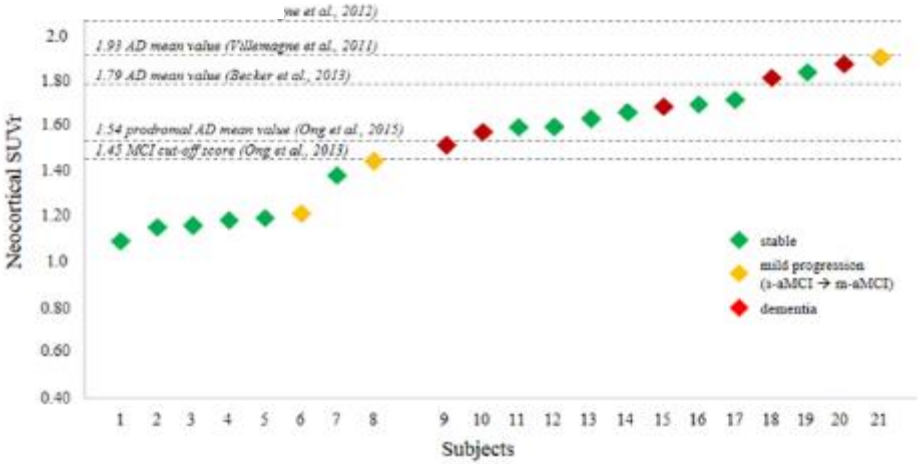
RESEARCH Open Access

A biomarker study in long-lasting amnestic mild cognitive impairment

Chiara Cerami[1,2*], Alessandra Dodich[1,2], Sandro Iannaccone[2], Giuseppe Magnani[3], Roberto Santangelo[3], Luca Presotto[4], Alessandra Marcone[2], Luigi Gianolli[4], Stefano F. Cappa[5,6] and Daniela Perani[1,4,7]

30 subjects





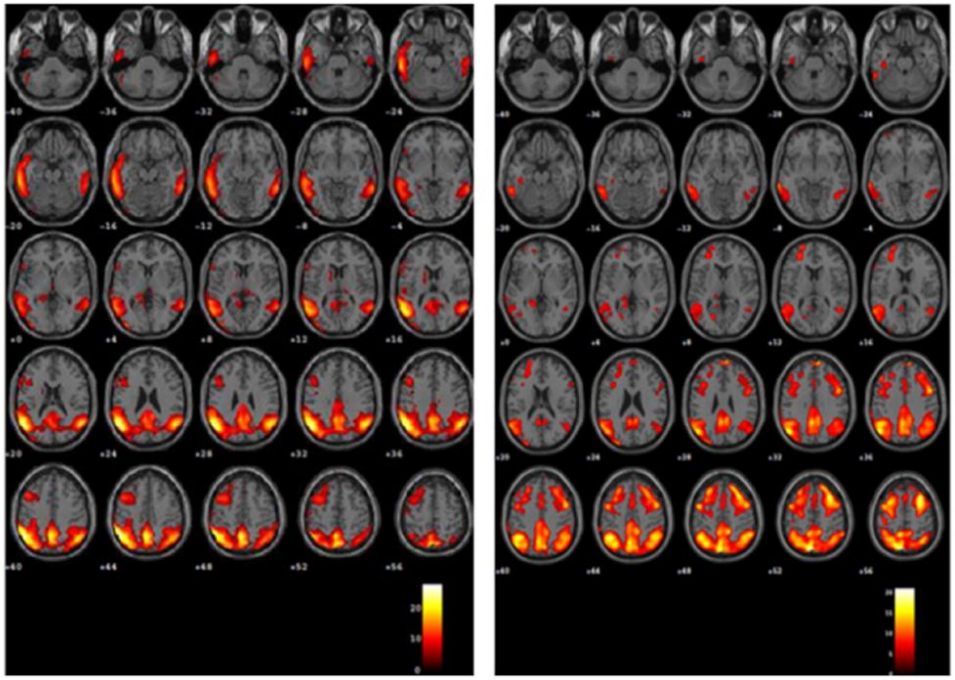
Alternative pathological conditions, such as AGD, primary age-related tauopathy or age-related TDP-43 proteinopathy, known to spread throughout the medial temporal lobe and limbic system structures

Cerami et al., Alzh Res Ther 2018

NeuroImage: Clinical

FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicentre MCI cohort

Silvia Paola Caminiti[a,b], Tommaso Ballarini[b], Arianna Sala[a,b], Chiara Cerami[b,c], Luca Presotto[b], Roberto Santangelo[d], Federico Fallanca[c], Emilia Giovanna Vanoli[c], Luigi Gianolli[c], Sandro Iannaccone[c], Giuseppe Magnani[d], Daniela Perani[a,b,e,*], BIOMARKAPD Project



Pattern FDG-PET tipico per Alzheimer's disease (AD)

biomarcatore di rischio di progressione ad AD demenza

METODI

SOGGETTI: 86 aMCI

- **Neurologia, Ospedale San Raffaele, Milano**
- **Alzheimer's Disease Neuroimaging Initiative (ADNI)**

ASSESSMENT

- **Valutazione clinica e neuropsicologica alla baseline**
- **Storia clinica e Follow-up clinico (da 4 a 12 anni)**
- **Esame del liquor**
- **FDG-PET**
- **MRI (*esclusione di sclerosi ippocampale e malattia cerebrovascolare*)**

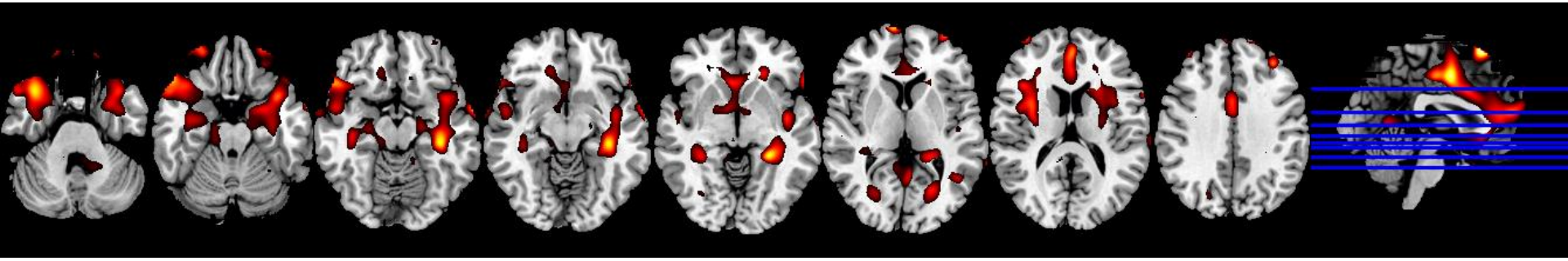
SAMPLE

Clinical demographic features

	Patients sample (n=86)
Female/male ratio	34/52
Age (mean ± SD)	74.59 ± 5.23
Years of education (mean ± SD)	13.82 ± 4.58
Disease duration at the first evaluation (mean ± SD)	**4.02±2.34**
Disease duration in years at the follow up (mean ±	**8.17±3.19 (Range: 4-19 Years)**
MMSE adjusted score at the first evaluation (mean ± SD)	**26.56±1.87**
MMSE adjusted score at follow-up (mean ± SD)	**25.59±2.35**
AT(N) classification: **A+T+(N+) or A+T-(N+)**	45
A-T-(N+) or A-T+(N+)	41
CSF Aβ42 low levels	45
CSF t-Tau high level	42
CSF p-Tau high level	54

Single Subject

MCI amnestic patient

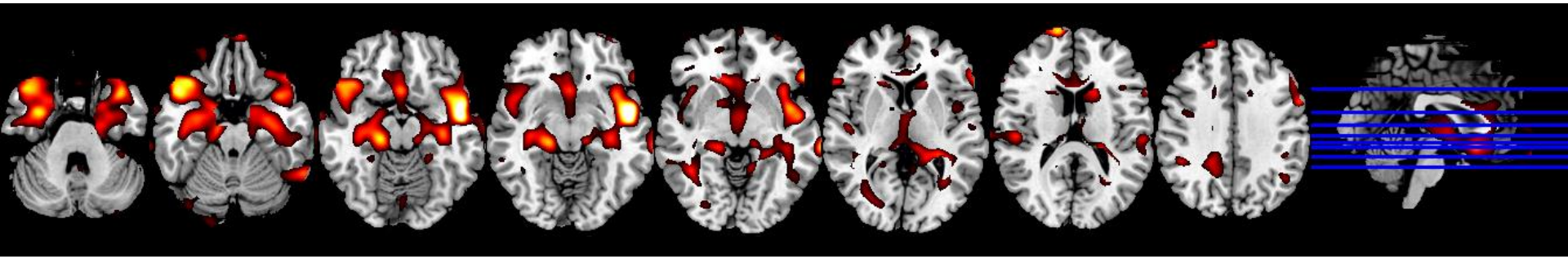


Age: 68
MMSE score, baseline: 29
MMSE score, last follow up: 29
Disease duration: 8 Years

CSF:
Aβ normal
Ttau pathologic
Ptau pathologic

Single Subject

MCI amnestic patient

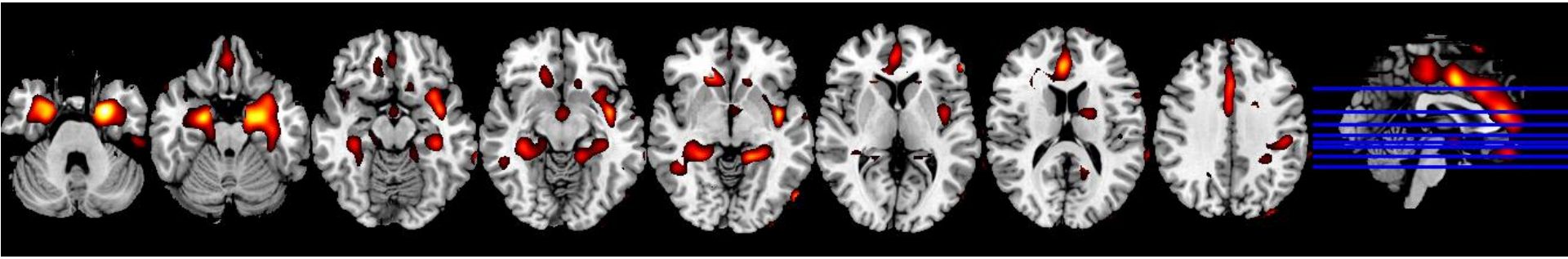


Age: 74
MMSE score, baseline: 26
MMSE score, last follow up: 27
Disease duration: 8 Years

CSF:
Aβ pathologic
Ttau pathologic
Ptau pathologic

Single Subject

MCI amnestic patient

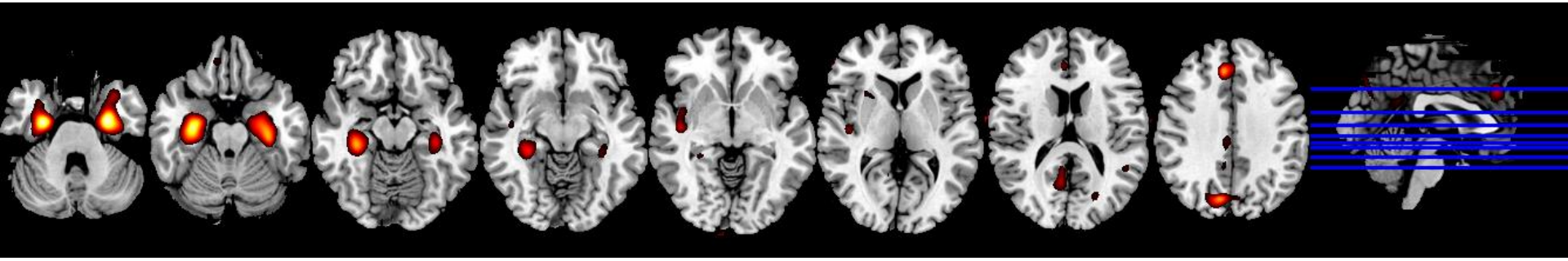


Age: 77
MMSE score, baseline: 26
MMSE score, last follow up: 24
Disease duration: 9 Years

CSF:
Aβ pathologic
Ttau pathologic
Ptau pathologic

Single Subject

MCI amnestic patient

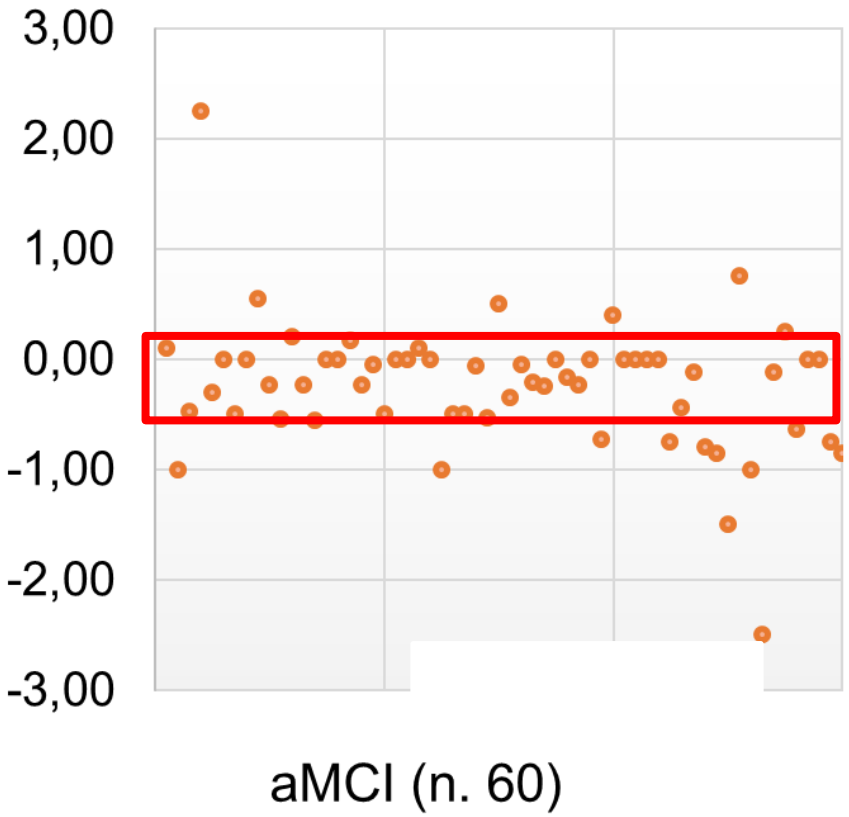


Age: 79
MMSE score, baseline: 26
MMSE score, last follow up: 24
Disease duration: 7 Years

CSF:
Aβ negative
Ttau negative
Ptau negative

Nessun aMCI progredisce a demenza

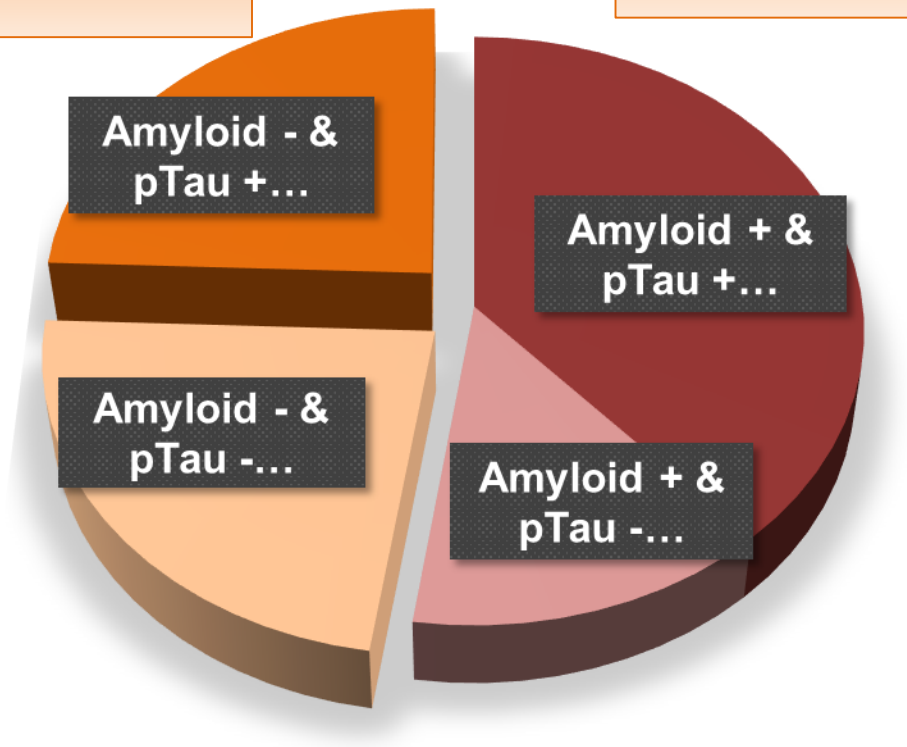
INDICE DI PROGRESSIONE
(MMSE follow-up – MMSE baseline)
anni di follow-up



According to FDG PET and CSF values

N+ and Non AD pathological changes 48%

N+ and AD pathological changes 52%



FDG-PET Sensitivity for Clinical Stability

$$\text{Sensitivity} = \frac{\text{Number of true positive}}{\text{Total number of patients}}$$

$$\text{Sensitivity} = \frac{80}{86} = 93.02\%$$

Only 6 out of 86 aMCI subjects presented abnormal MMSE score at last follow-up

CONCLUSIONI

Soggetti con aMCI e pattern FDG-PET temporo-mesiale e limbico mostrano un'evoluzione clinica benigna, caratterizzata da non progressione a demenza

I biomarcatori liquorali non contribuiscono alla diagnosi e sono ininfluenti nel caratterizzare la stabilità clinica

L'unico biomarcatore con valore diagnostico e prognostico predittivo di stabilità è il metabolismo cerebrale valutato con FDG-PET

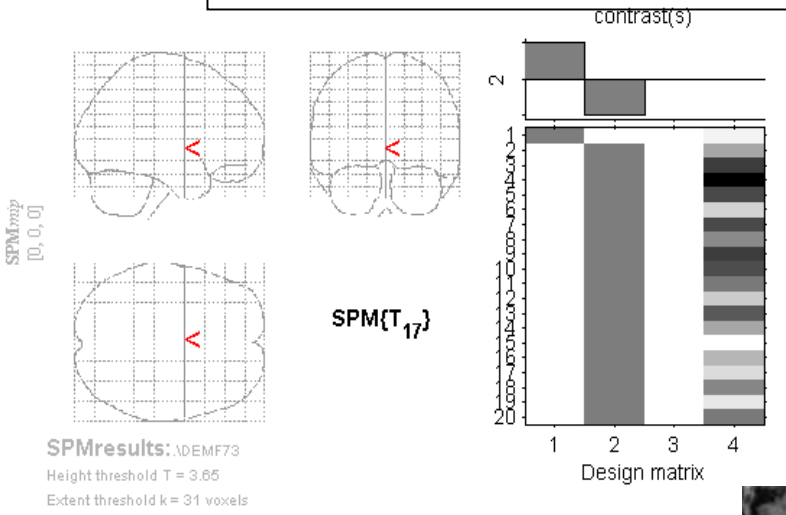
Eziologie possibili: limbic predominant age related TDP-43 encephalopathy, argyrophilic grain disease, primary age related tauopathy

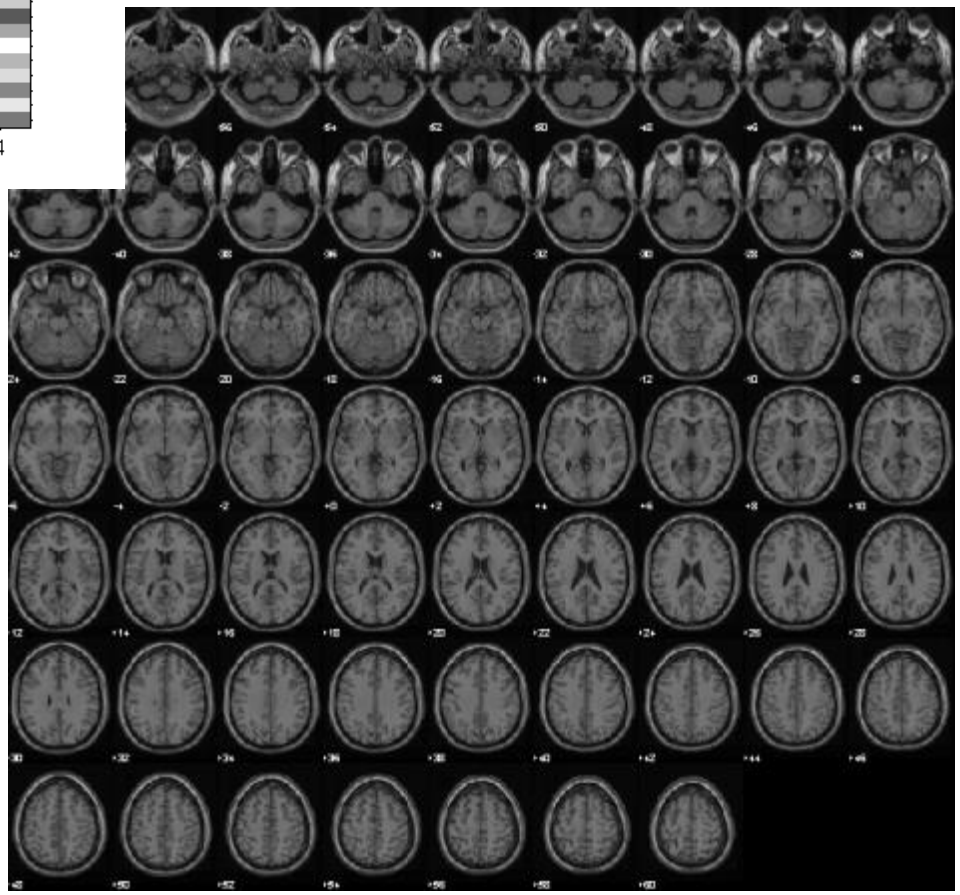
Crary et al., Acta Neurop 2014; Ferrer et al., Brain 2008; Cerami et al. 2018, Nelson et al., Brain 2019

Diagnostic challenge

Exclusionary role

aMCI ♀ 62 years old





NO Neurodegenerative disease exclusionary role!

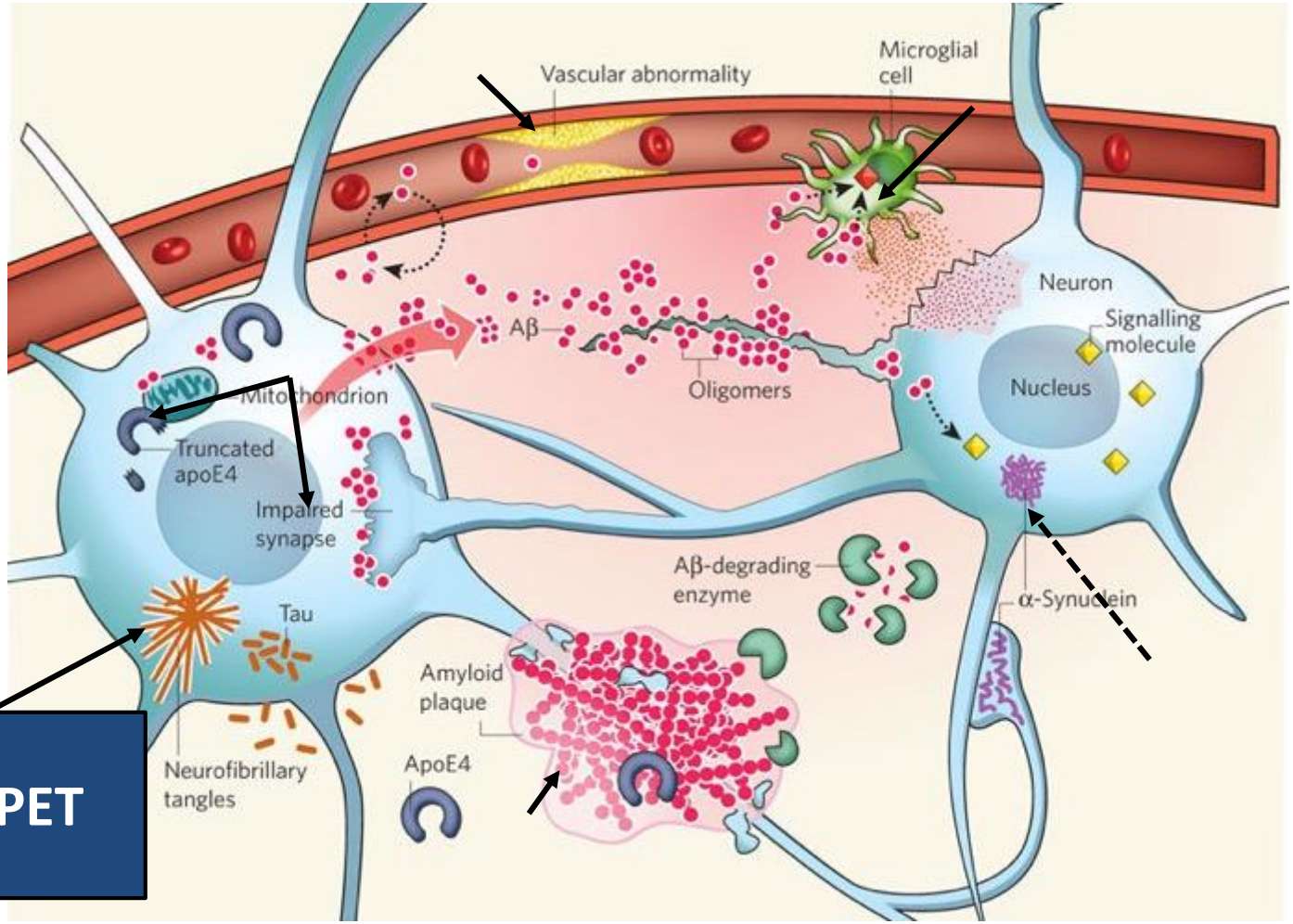
FDG PET EXCLUSIONARY ROLE

A crucial aspect that posits FDG PET measures as the most supportive finding of neural dysfunction and neurodegeneration is that **clinical symptoms never occur without brain metabolic decreases**, the extent of which is related to the severity of cognitive impairment

All the above and the high specificity of FDG PET in AD, FTLD and DLB implies that **a negative, or normal scan in the presence of the suspicion of dementia makes a diagnosis of a neurodegenerative disease very unlikely**

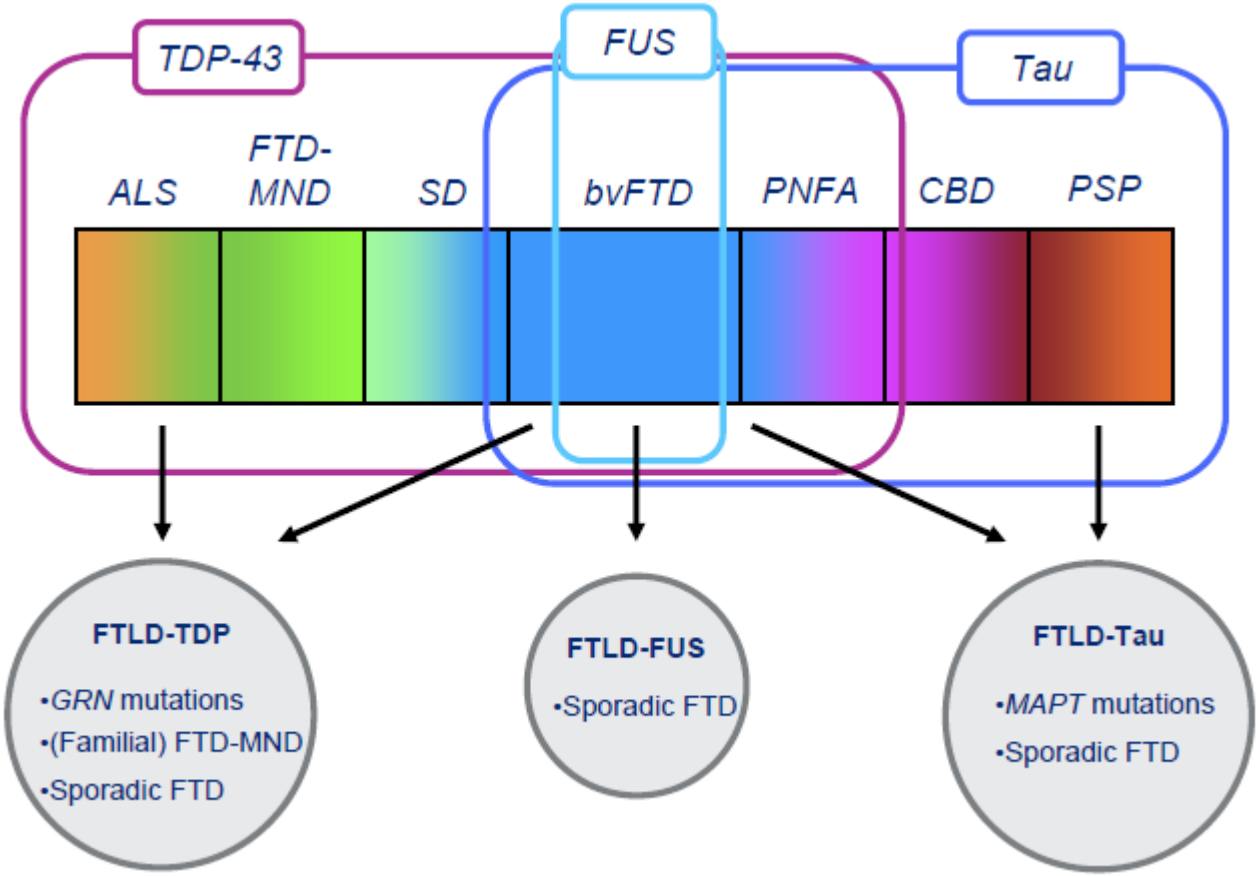
The accuracy measures available with FDG PET near the time of initial diagnosis of dementia is similar to longitudinal clinical diagnosis over 3–4 years, thus **in the context of initial diagnosis, the exclusionary role of FDG PET is especially important** in younger subjects with a suspicion of neurodegenerative disease.

Jagust et al., 2012, Perani 2014, Iaccarino et al, 2018


Vascular abnormality
Microglial cell
Neuron
Signalling molecule
Nucleus
Aβ
Oligomers
Mitochondrion
Truncated apoE4
Impaired synapse
Aβ-degrading enzyme
α-Synuclein
Tau
Amyloid plaque
ApoE4
Neurofibrillary tangles

Tau-PET

FTD spectrum



Seelaar et al., 2013

BRAIN
A JOURNAL OF NEUROLOGY

Brain 2014: 137; 1570–1578

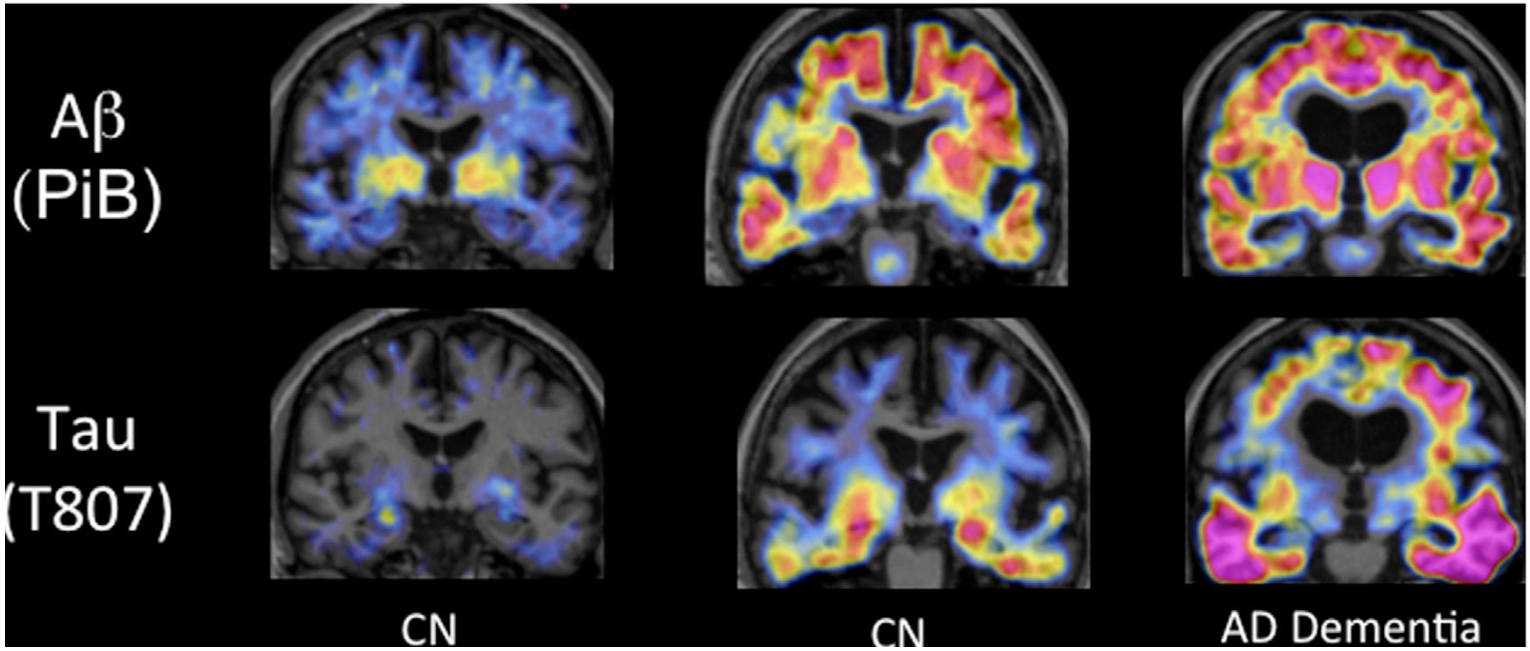
SCIENTIFIC COMMENTARIES

Time for tau

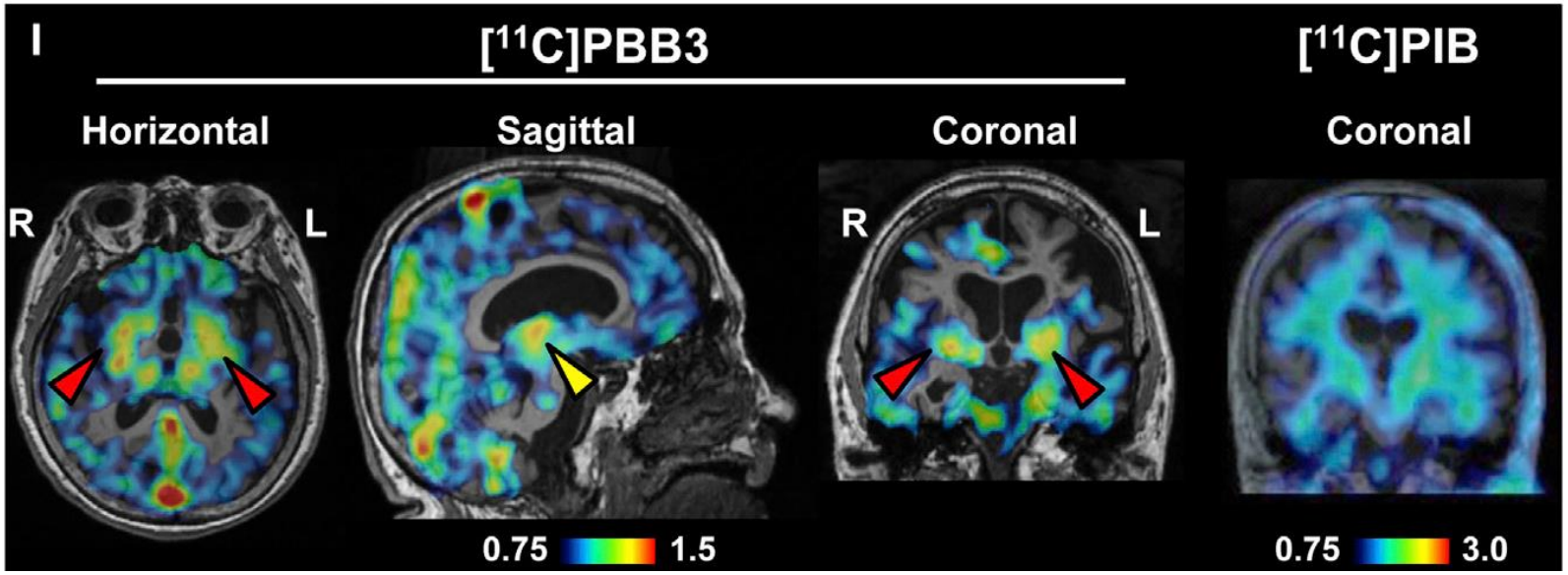
We may open up new avenues to the study of AD and non-AD tauopathies and chronic traumatic encephalopathy

The pace of scientific discovery is accelerating and the end result will be more tools and more information that should result in more effective treatments

William Jagust



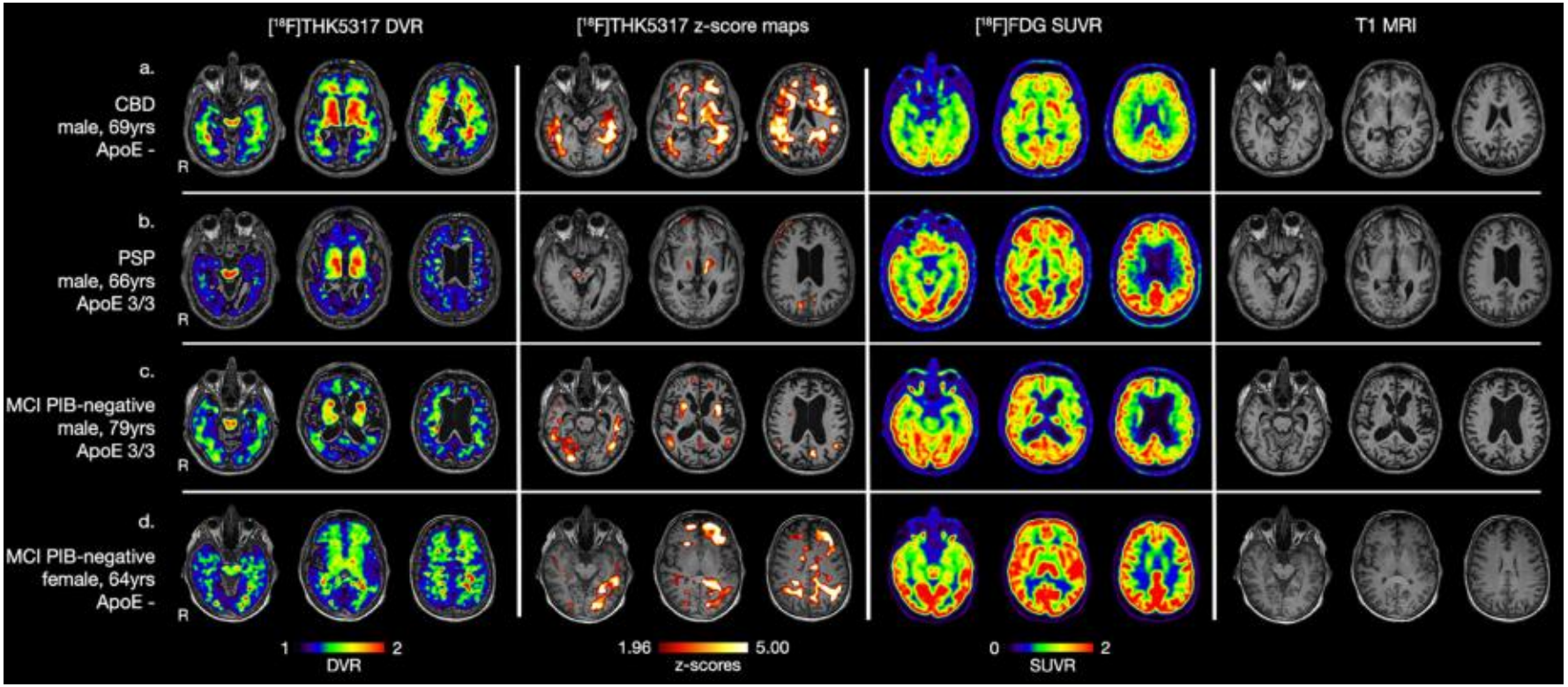
AD



CBD

Maruyama et al. Neuron 2013

18F]THK5317 tau-PET in non-Alzheimer's disease dementia



Chiotis et al. 2016

doi:10.1093/brain/awz268 BRAIN 2019: 142; 3230–3242 | 3230

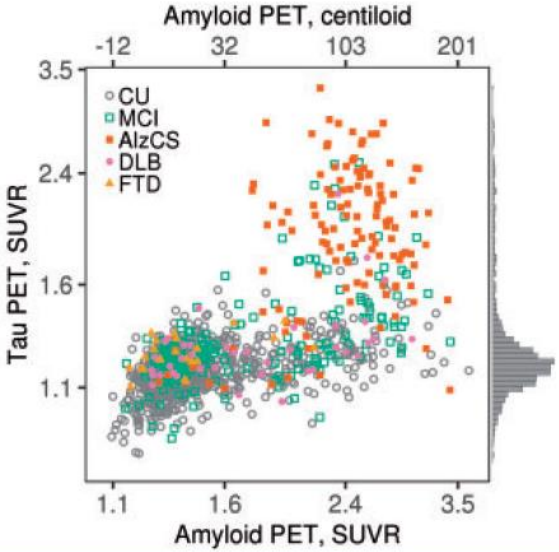
BRAIN
A JOURNAL OF NEUROLOGY

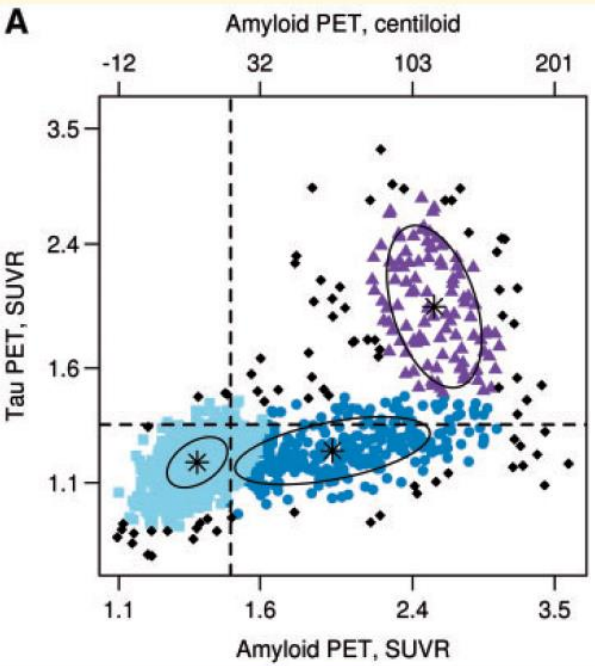
The bivariate distribution of amyloid-β and tau: relationship with established neurocognitive clinical syndromes

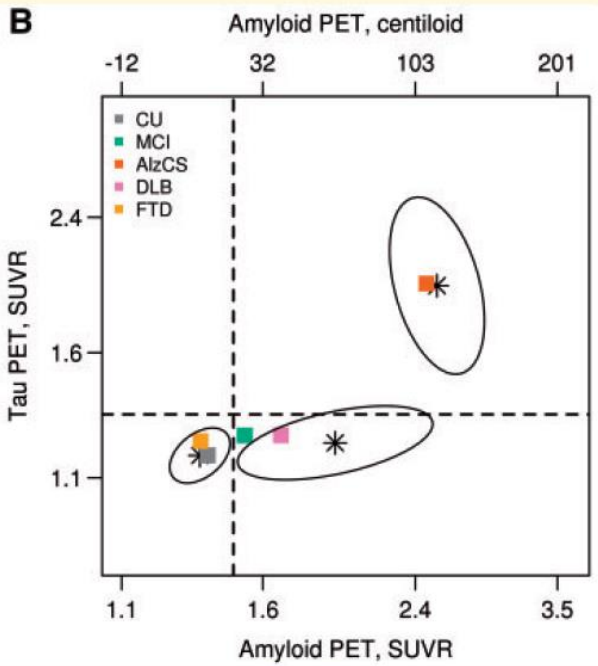
Clifford R. Jack, Jr,[1] Heather J. Wiste,[2] Hugo Botha,[3] Stephen D. Weigand,[2] Terry M. Therneau,[2] David S. Knopman,[3] Jonathan Graff-Radford,[3] David T. Jones,[1,3] Tanis J. Ferman,[4] Bradley F. Boeve,[3] Kejal Kantarci,[1] Val J. Lowe,[5] Prashanthi Vemuri,[1] Michelle M. Mielke,[6] Julie A. Fields,[7] Mary M. Machulda,[7] Christopher G. Schwarz,[1] Matthew L. Senjem,[1] Jeffrey L. Gunter[1] and Ronald C. Petersen[3]

Table 1 Demographic characteristics of study participants

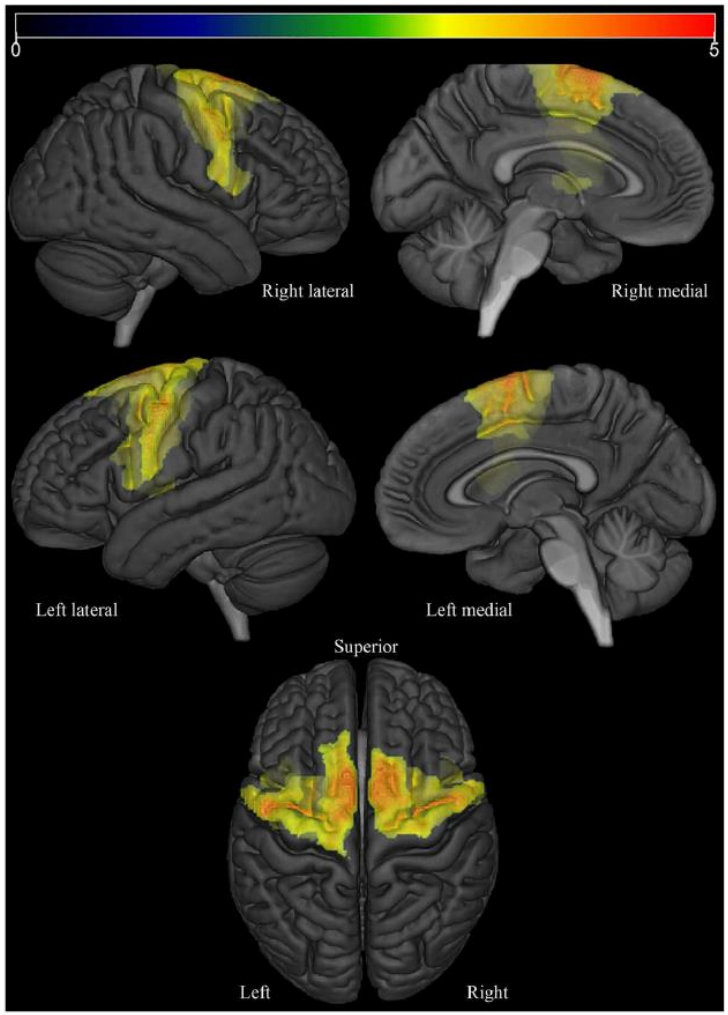
Characteristic	CU	MCI	AlzCS	DLB	FTD
Number of subjects	976	182	123	39	23
Study, *n* (%)					
MCSA	903 (93)	92 (51)	8 (7)	3 (8)	0 (0)
ADRC[a]	73 (7)	90 (49)	115 (93)	36 (92)	23 (100)


Amyloid PET, centiloid
-12
32
103
201
3.5
2.4
1.6
1.1
CU
MCI
AlzCS
DLB
FTD
Tau PET, SUVR
1.1
1.6
2.4
3.5
Amyloid PET, SUVR


A
Amyloid PET, centiloid
-12
32
103
201
3.5
2.4
1.6
1.1
Tau PET, SUVR
1.1
1.6
2.4
3.5
Amyloid PET, SUVR

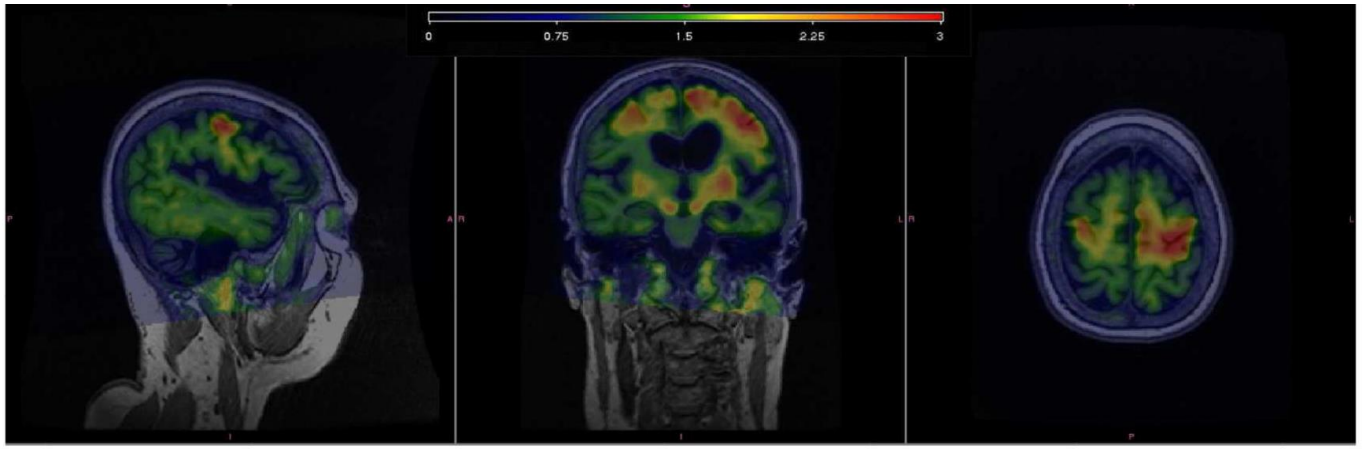

B
Amyloid PET, centiloid
-12
32
103
201
CU
MCI
AlzCS
DLB
FTD
2.4
1.6
1.1
Tau PET, SUVR
1.1
1.6
2.4
3.5
Amyloid PET, SUVR

Tau-PET imaging with [18F]AV-1451 in Primary Progressive Apraxia of Speech

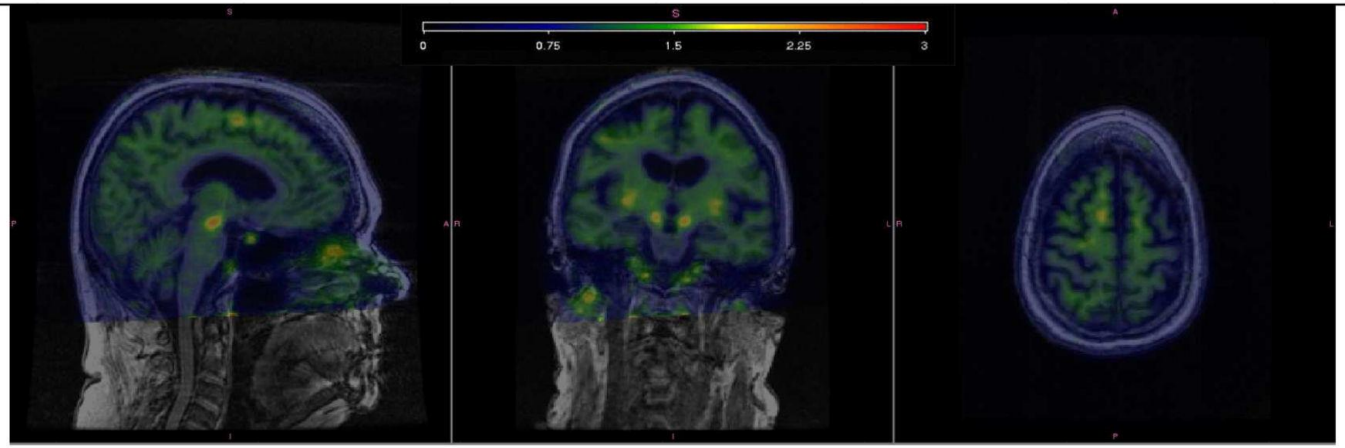


This cross-sectional study demonstrates that elevated tau tracer uptake is observed using [18F]AV-1451 in PPAOS

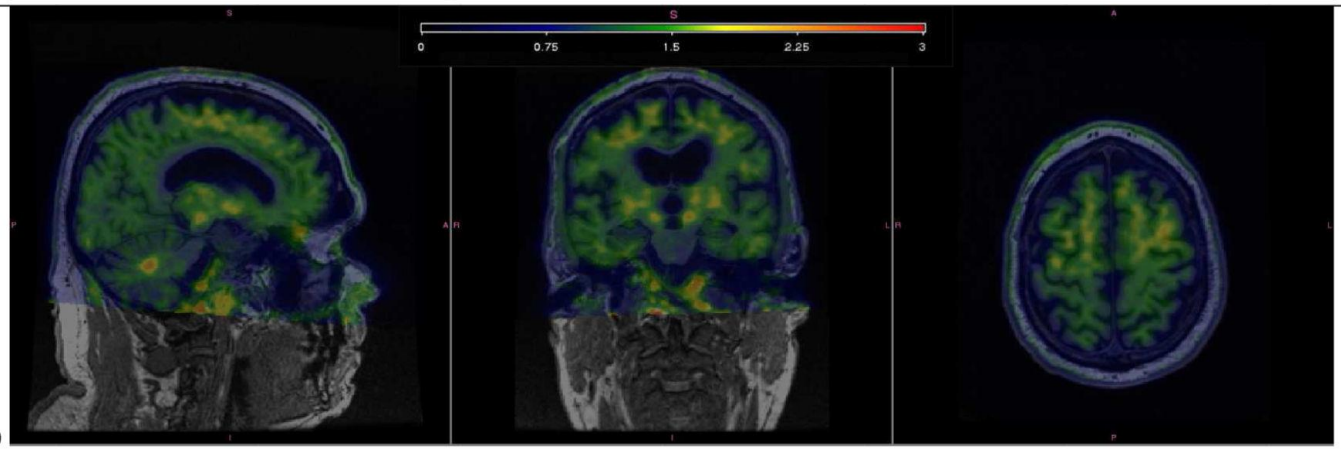
Utianski et al. Cortex 2017



Patient 2 (PPAOS*a*)



Patient 9 (PPAOS)



Patient 14 (PPAOS)

Tsai *et al. Alzheimer's Research & Therapy* (2019) 11:13
https://doi.org/10.1186/s13195-019-0470-7

Alzheimer's
Research & Therapy

RESEARCH Open Access

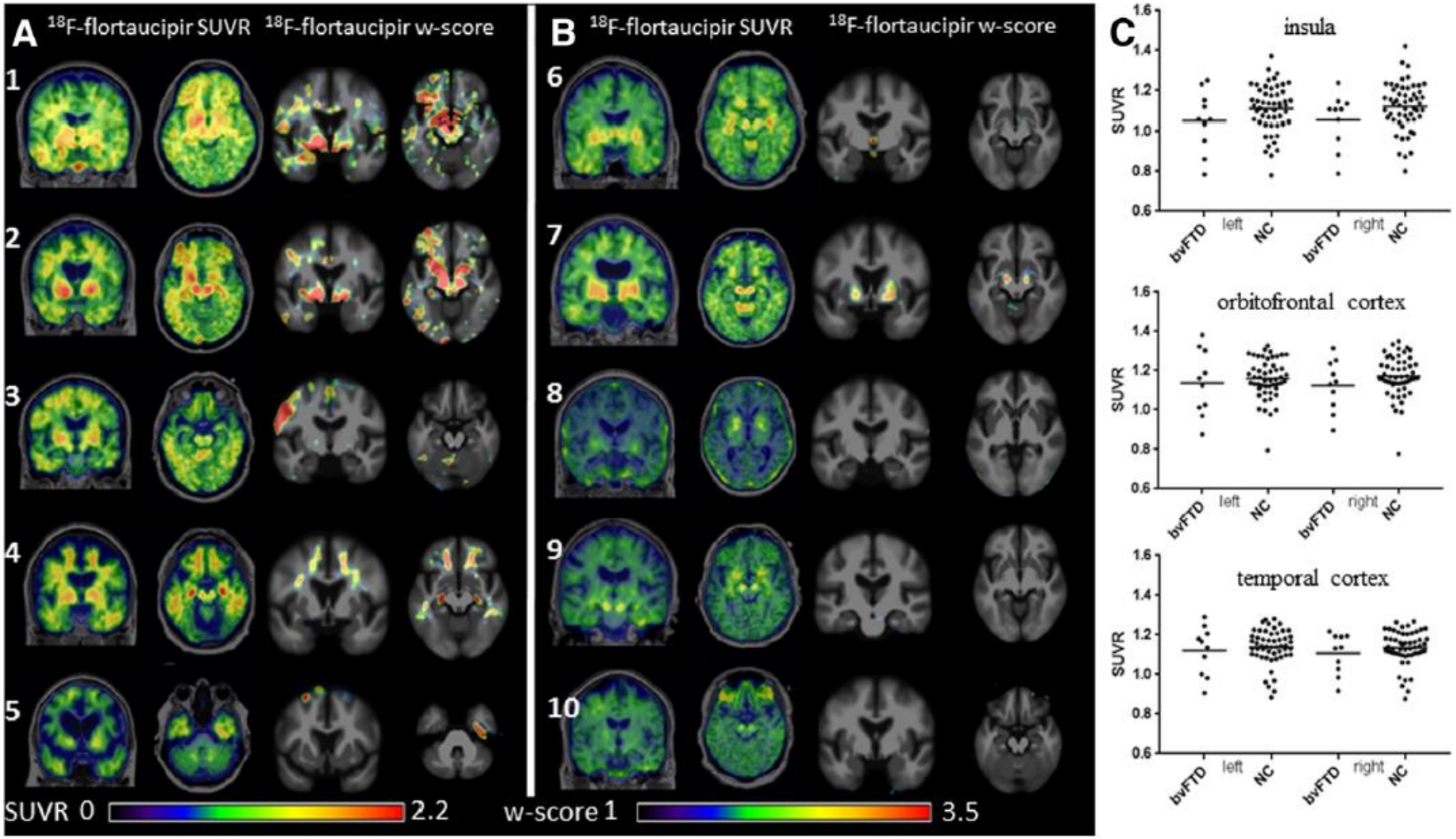
^{18}F-flortaucipir (AV-1451) tau PET in frontotemporal dementia syndromes

Richard M. Tsai[1*†], Alexandre Bejanin[1†], Orit Lesman-Segev[1], Renaud LaJoie[1], Adrienne Visani[1], Viktoriya Bourakova[1], James P. O'Neil[3], Mustafa Janabi[3], Suzanne Baker[3], Suzee E. Lee[1], David C. Perry[1], Lynn Bajorek[1], Anna Karydas[1], Salvatore Spina[1], Lea T. Grinberg[1], William W. Seeley[1], Eliana M. Ramos[4], Giovanni Coppola[4], Maria Luisa Gorno-Tempini[1], Bruce L. Miller[1], Howard J. Rosen[1], William Jagust[2,3], Adam L. Boxer[1] and Gil D. Rabinovici[1,2]

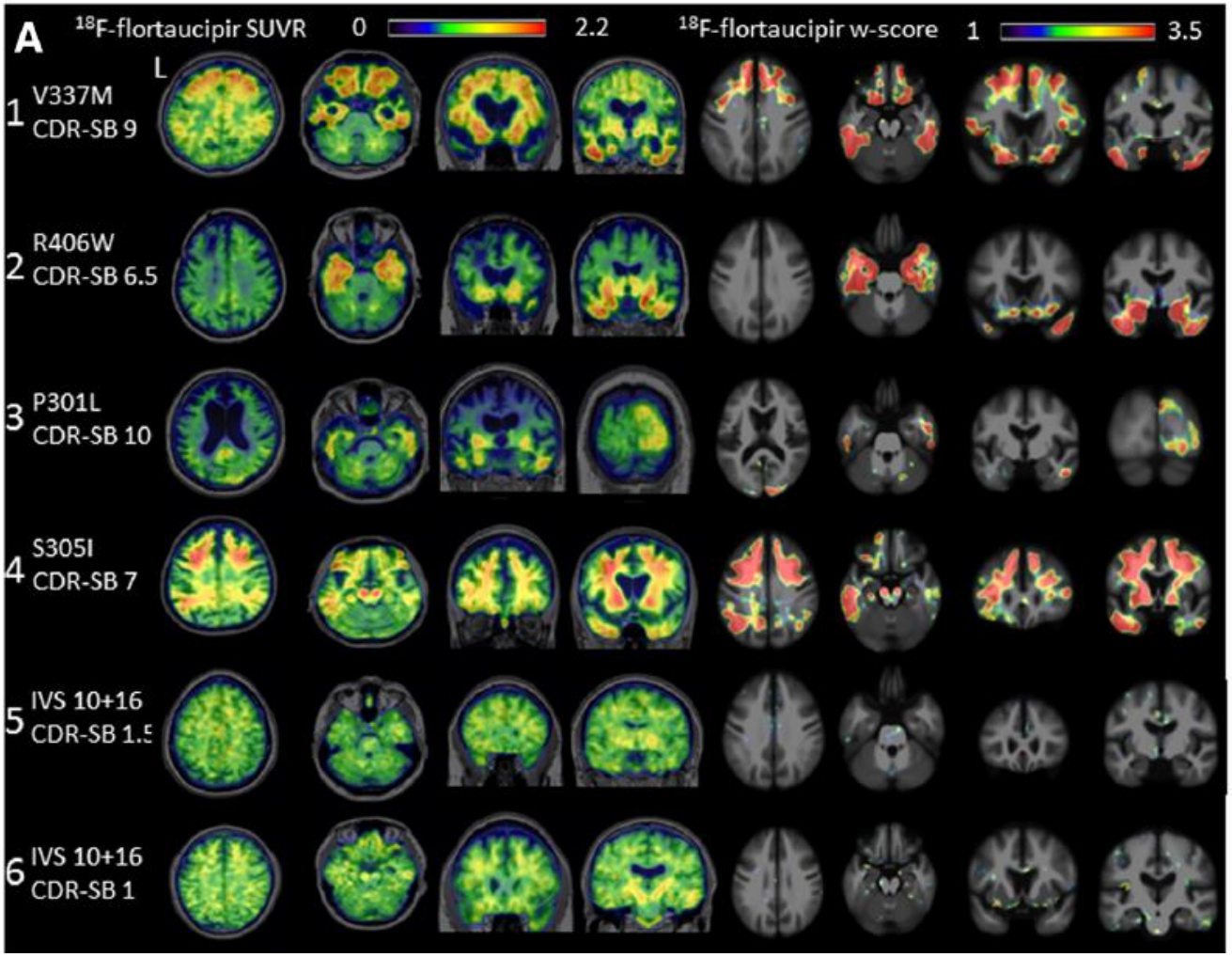
Conclusions: 18F-flortaucipir in patients with FTD and predicted tauopathy or TDP-43 pathology demonstrated **limited sensitivity and specificity**

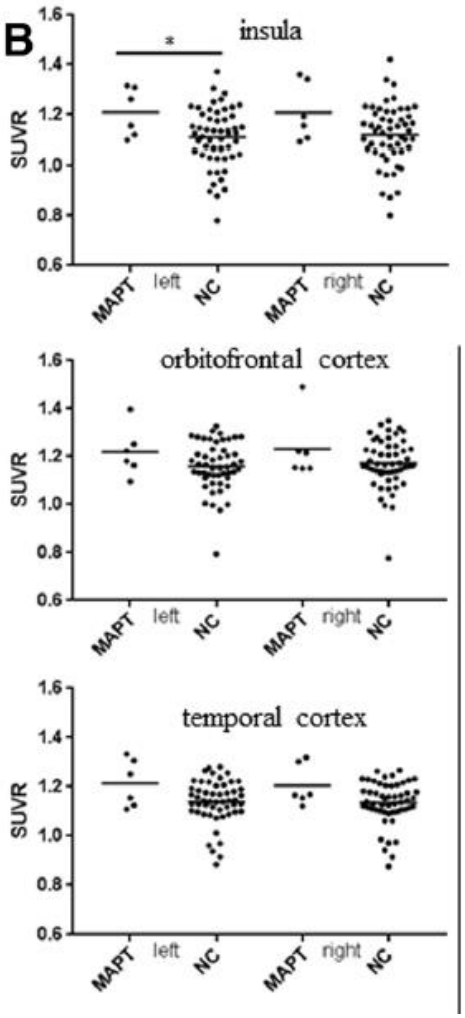
Further postmortem pathological confirmation and development of FTD tau-specific ligands are needed

bv FTD

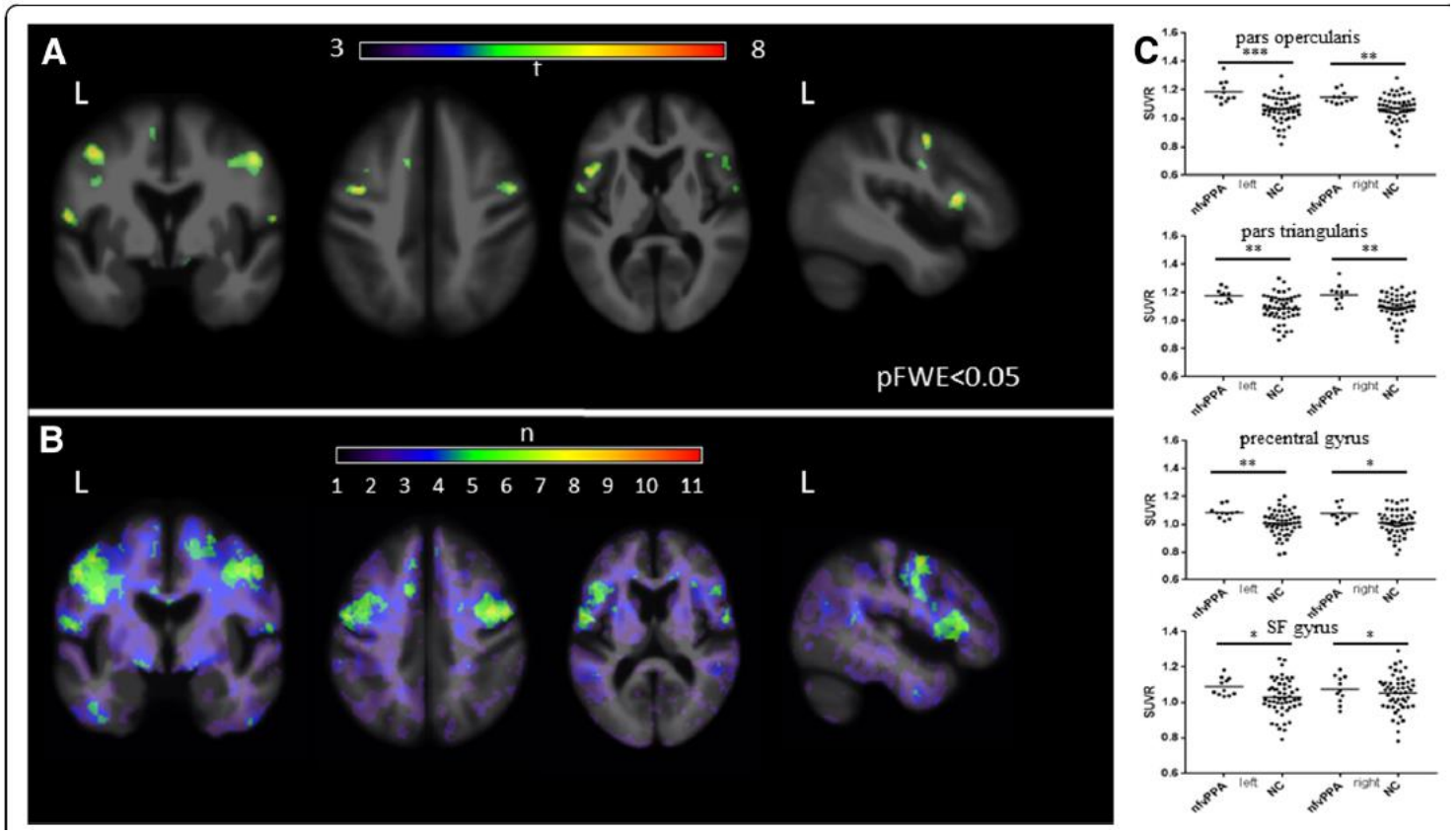

A
18F-flortaucipir SUVR
18F-flortaucipir w-score
1
2
3
4
5
B
18F-flortaucipir SUVR
18F-flortaucipir w-score
6
7
8
9
10
SUVR 0
2.2
w-score 1
3.5
C
insula
orbitofrontal cortex
temporal cortex
SUVR
1.6
1.4
1.2
1.0
0.8
0.6
bvFTD
left
NC
bvFTD
right
NC

MAPT

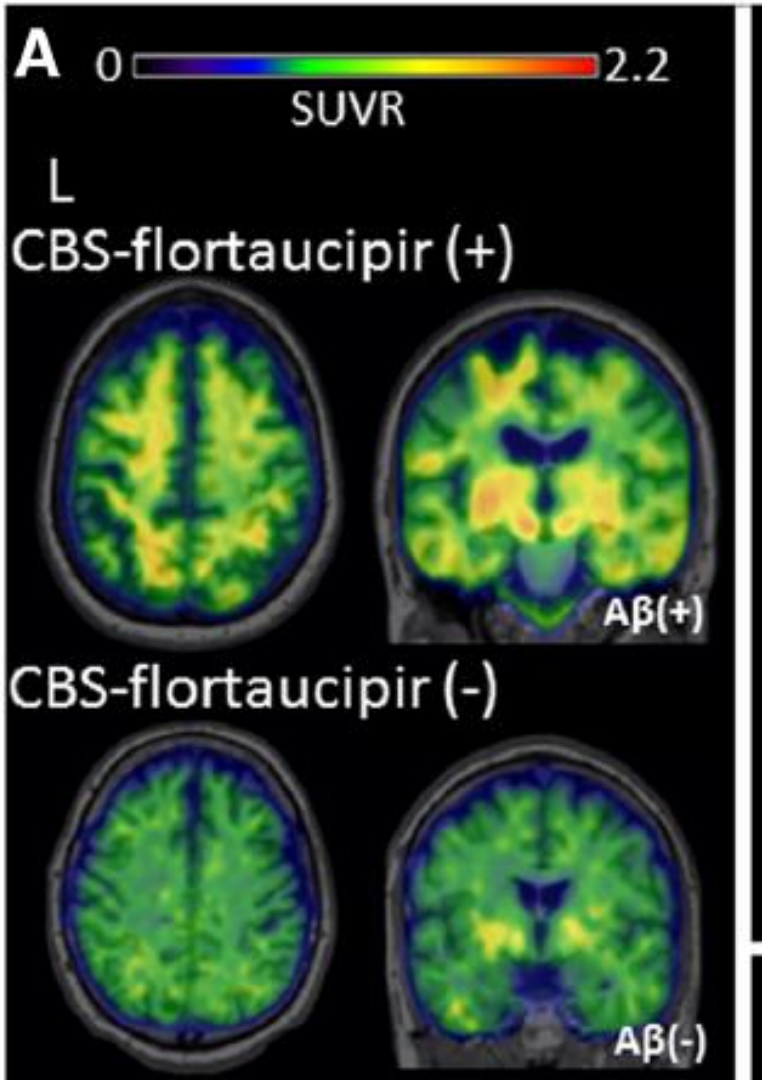

A
18F-flortaucipir SUVR
0
2.2
18F-flortaucipir w-score
1
3.5
L
1 V337M CDR-SB 9
2 R406W CDR-SB 6.5
3 P301L CDR-SB 10
4 S305I CDR-SB 7
5 IVS 10+16 CDR-SB 1.5
6 IVS 10+16 CDR-SB 1

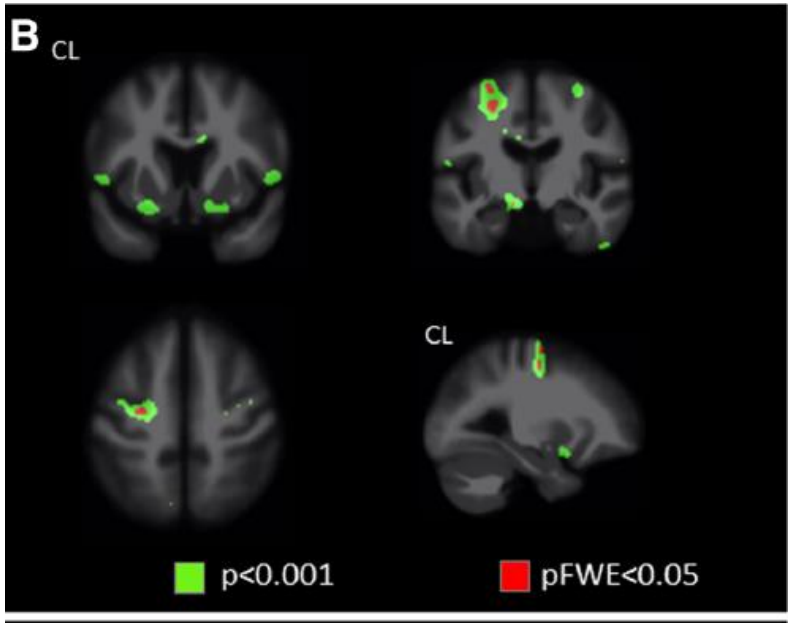

B
insula
orbitofrontal cortex
temporal cortex
SUVR
1.6
1.4
1.2
1.0
0.8
0.6
*
MAPT
left
NC
MAPT
right
NC

Nfv PPA


A
3
t
8
L
L
pFWE<0.05
B
n
1 2 3 4 5 6 7 8 9 10 11
L
L
C
pars opercularis
***
**
pars triangularis
**
**
precentral gyrus
**
*
SF gyrus
*
*
SUVR
nfvPPA
left
NC
nfvPPA
right
NC

CBS


A
0
2.2
SUVR
L
CBS-flortaucipir (+)
Aβ(+)
CBS-flortaucipir (-)
Aβ(-)


B
CL
CL
p<0.001
pFWE<0.05

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Pathologic correlations of [F-18]-AV-1451 imaging in non-Alzheimer tauopathies

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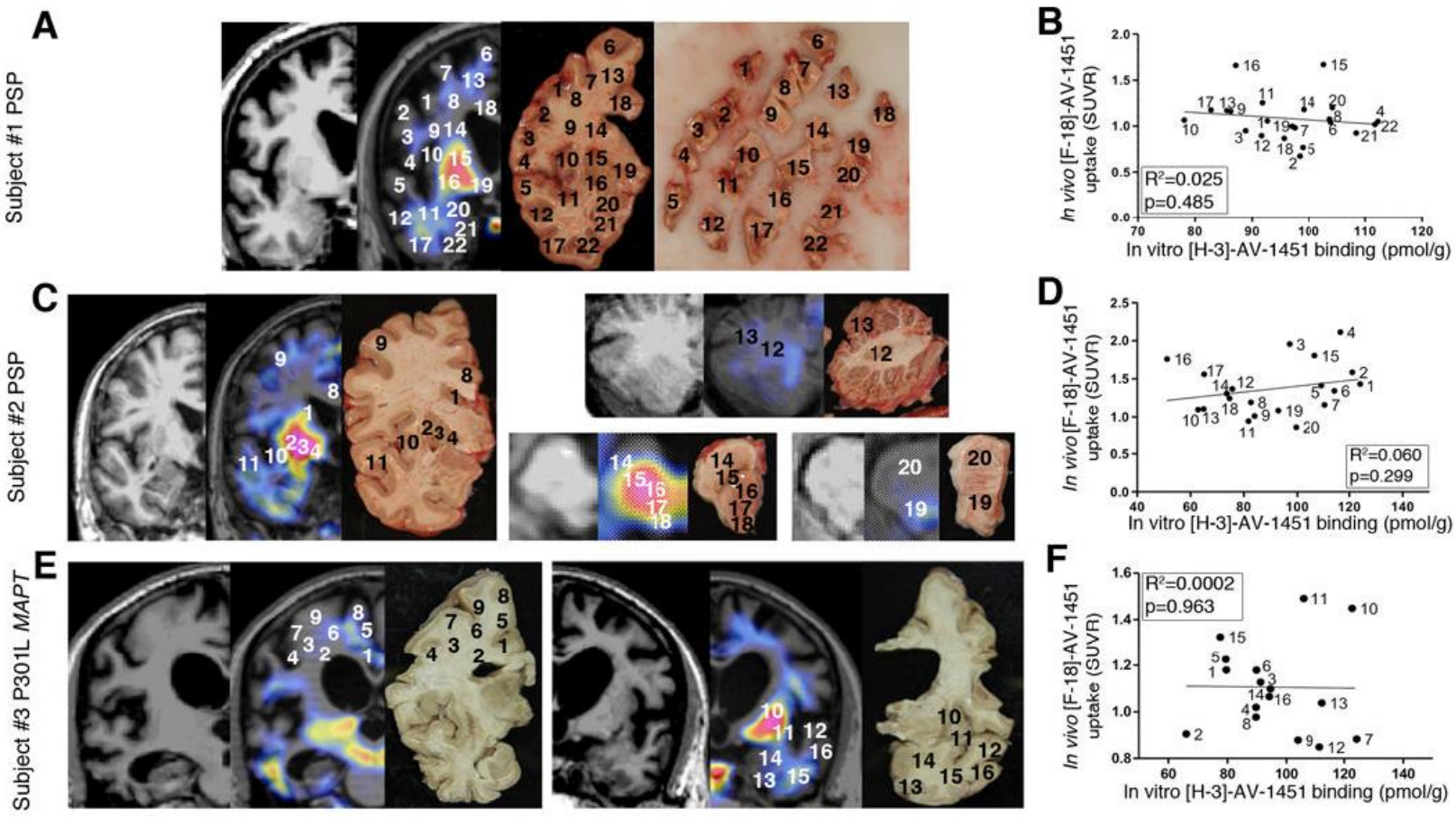
Interpretation AV-1451 may have **limited utility** for in vivo selective and reliable detection of tau aggregates in these non-Alzheimer tauopathies

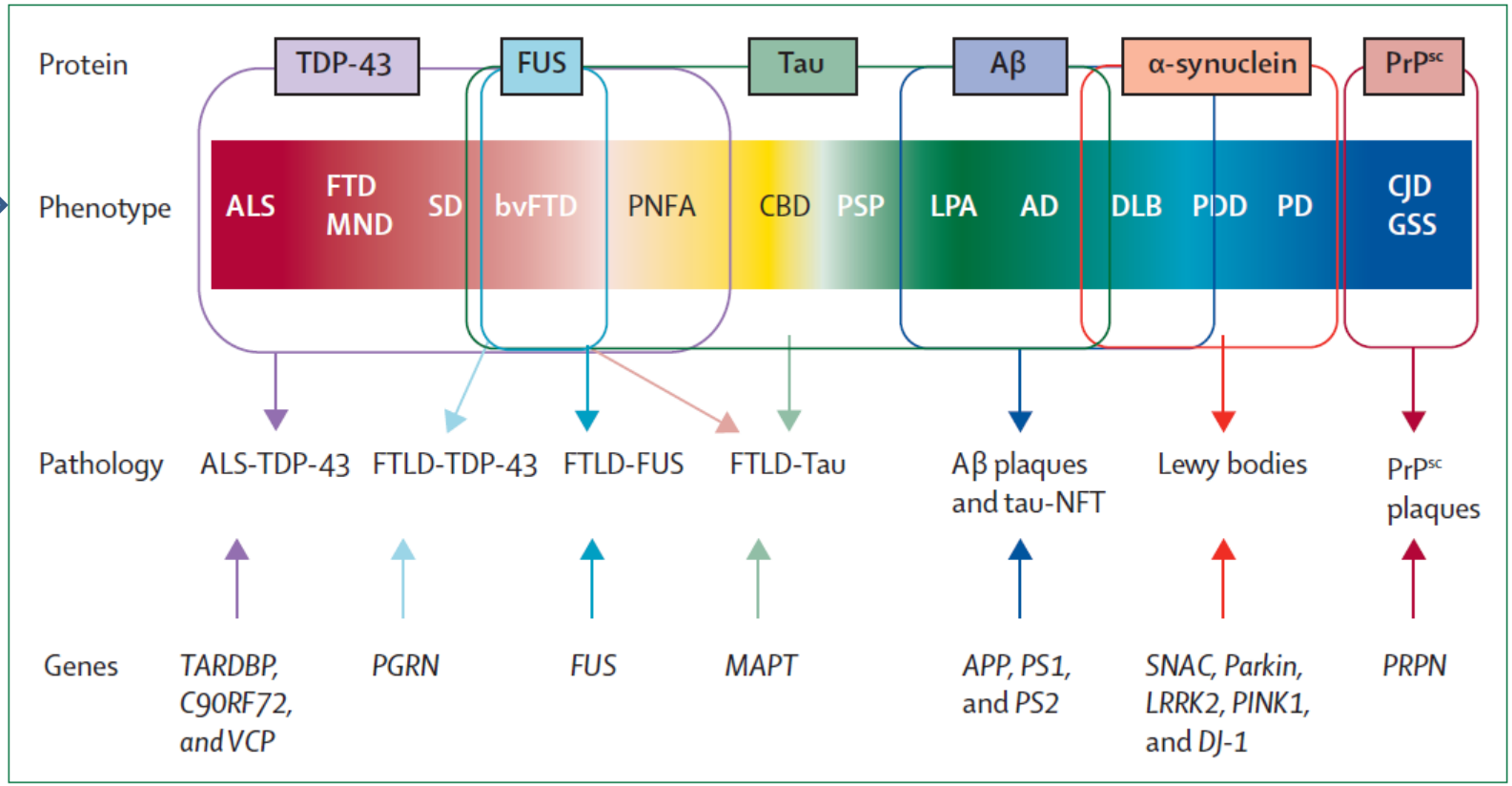


Images from coronal brain sections of MRI (left) and their corresponding [F-18]-AV-1451 PET scans (middle) and autopsy tissue blocks (right)

Pros and Cons

Tau aggregates	Tracers	Strengths	Weaknesses	Technical caveats
• AD dementia • MCI • DLB • CBD • PSP • CTE • DS • Genetic FTD • Healthy aging	• [11C]PBB3 • **[18F]Flortaucipir** • [18F]THK family	• *in vivo* detection of brain deposition of neurofibrillary tangles in AD, consistent with *post-mortem* autopsy findings • Tight relationships with ND and cognitive impairment in AD • track AD disease progression • evaluate tau therapies in clinical trials	• Presents non-specific binding in choroid plexus and neuromelanin-containing tissue • Pathologies characterized by predominant 4R tau and TDP-43 present weaker binding increases when compared to AD tauopathy • Medial temporal lobe tau accumulation is present in healthy aging • [18F]THK5351,non-specific binding to MAO-B	• Seems not to reach steady state in 100 minutes • Semi-quantified measurements are needed • Neuropathology studies are needed

PHENOTYPES, GENETICS, PROTEINOPATHIES IN NEURODEGENERATIVE DEMENTIA



Seelaar et al., J Neurol Neurosurg Psychiatry, 2011

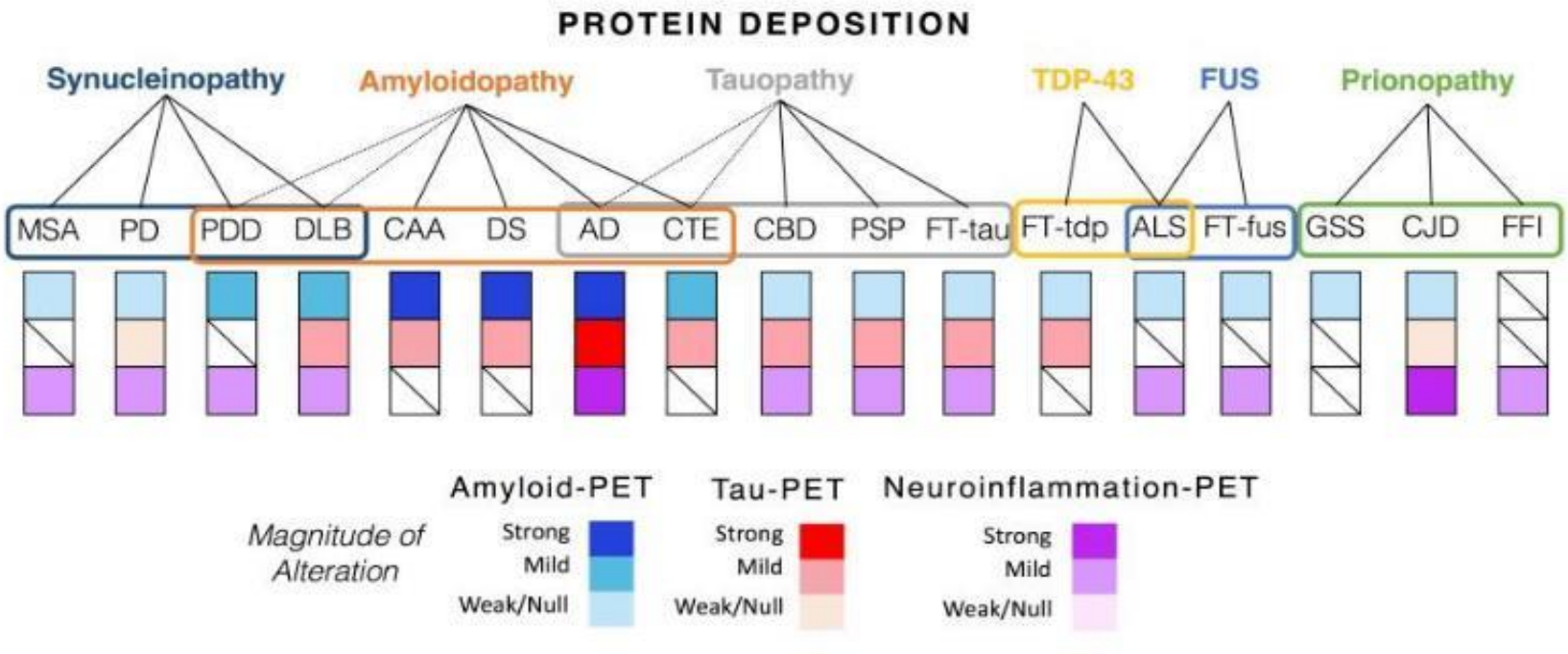
A NEW PERSPECTIVE

Last years are witnessing a rapid transition from a **clinical-based** to a **pathology-based classification** of neurodegenerative conditions, largely promoted by the **increasing availability of molecular neuroimaging biomarkers**

This implementation promotes a **spectrum-approach to neurodegenerative conditions**, based on **pathology subtypes** and **clinical endophenotype heterogeneity**

Perani et al., and IMBI Consortium Alzh. & Dem., 2019

JPND research
EU Joint Programme – Neurodegenerative Disease Research



Descriptive meta-analysis from the relate literature
Color gradients index magnitude of alteration

A NEW PERSPECTIVE

This approach will enhance efforts to understand both the biology of Alzheimer's Disease as well as the multifactorial etiology of other dementias, which has been obscured to some extent in the past by equating the PET protein molecular biomarker role to an effective diagnostic tool

Together with methodological challenges in the production of these tracers, their optimal quantification and standardization procedures, and their evidence-based clinical utility

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THANK YOU
FOR YOUR ATTENTION

Imaging imagination. Shown is part of the engraving, "The Physician Curing Fantasy," by Mathaus Greuter (1564–1638).