Integrated PET/MR scanner as reference imaging tool in the study of dementia: results from the PM-D project

Portoferraio, May 20th 2024

Marco Aiello

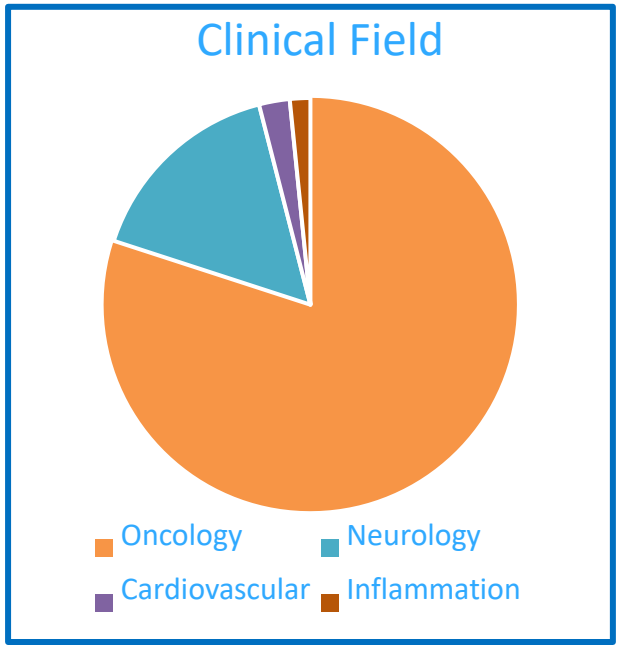
IRCCS SYNLAB SDN, Naples

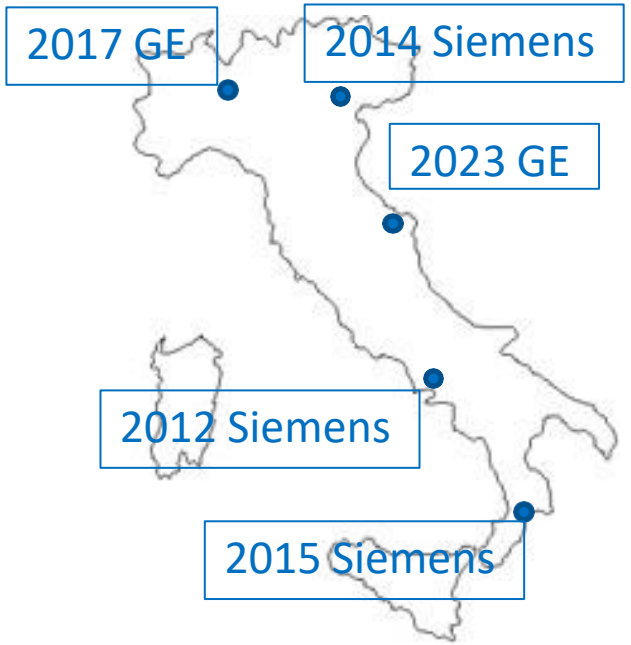
marco.aiello@synlab.it

SYNLAB IRCCS SDN

Intro

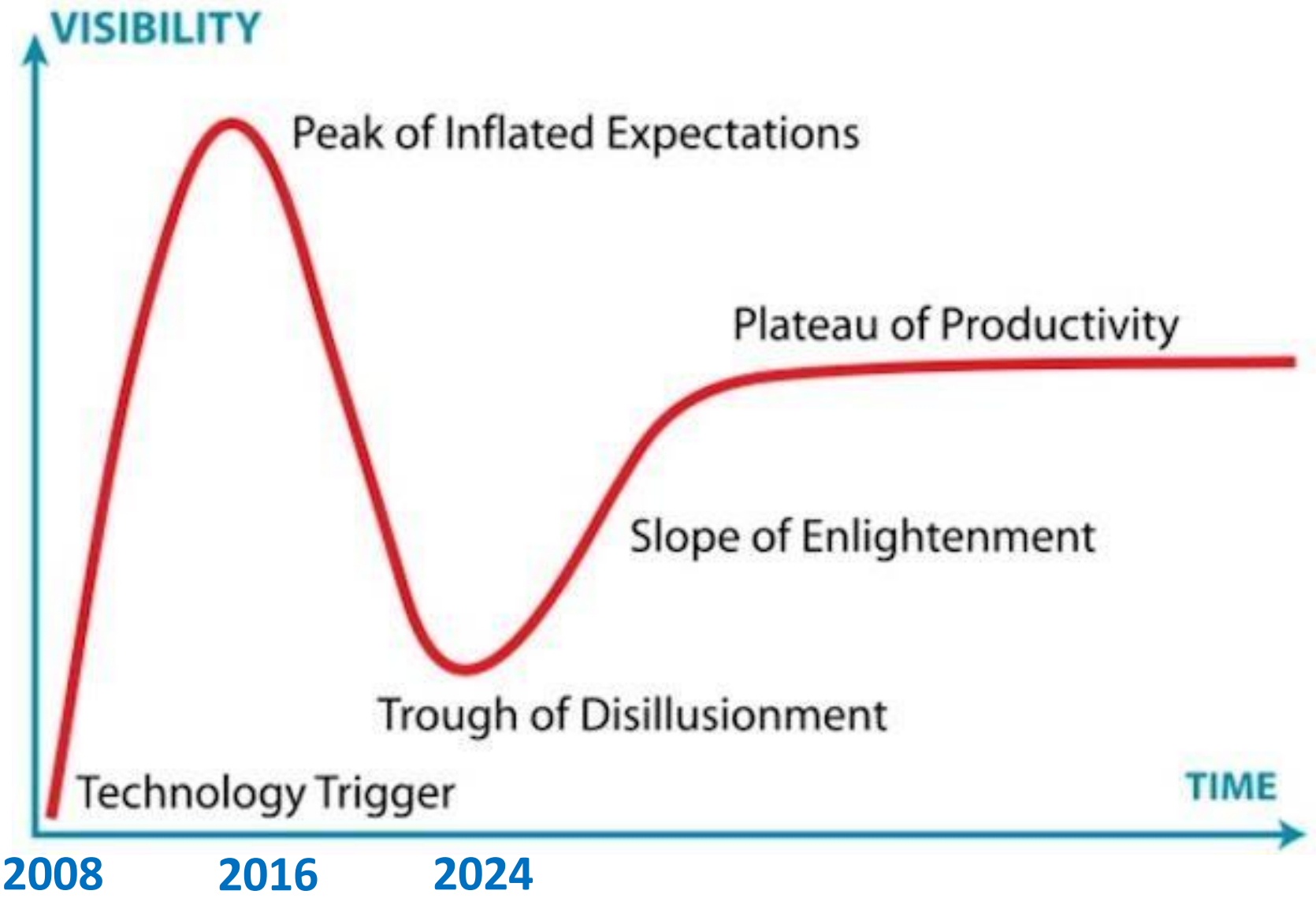
- IRCCS SYNLAB SDN - Research Institute for integrated diagnostics
- Our PET/MR: Biograph mMR VE11p
- 2012-2023: ≈ 4000 PET/MR exams





SYNLAB
IRCCS SDN

PET/MR: where are we at?



https://it.wikipedia.org/wiki/Hype_cycle

SYNLAB IRCCS SDN

Becker, M., & Garibotto, V. (2023). PET/MR Imaging in Clinical Practice: After Expectations and (Some) Disillusion, a Slope of Enlightenment. *Magnetic Resonance Imaging Clinics*, *31*(4), xv-xvi.

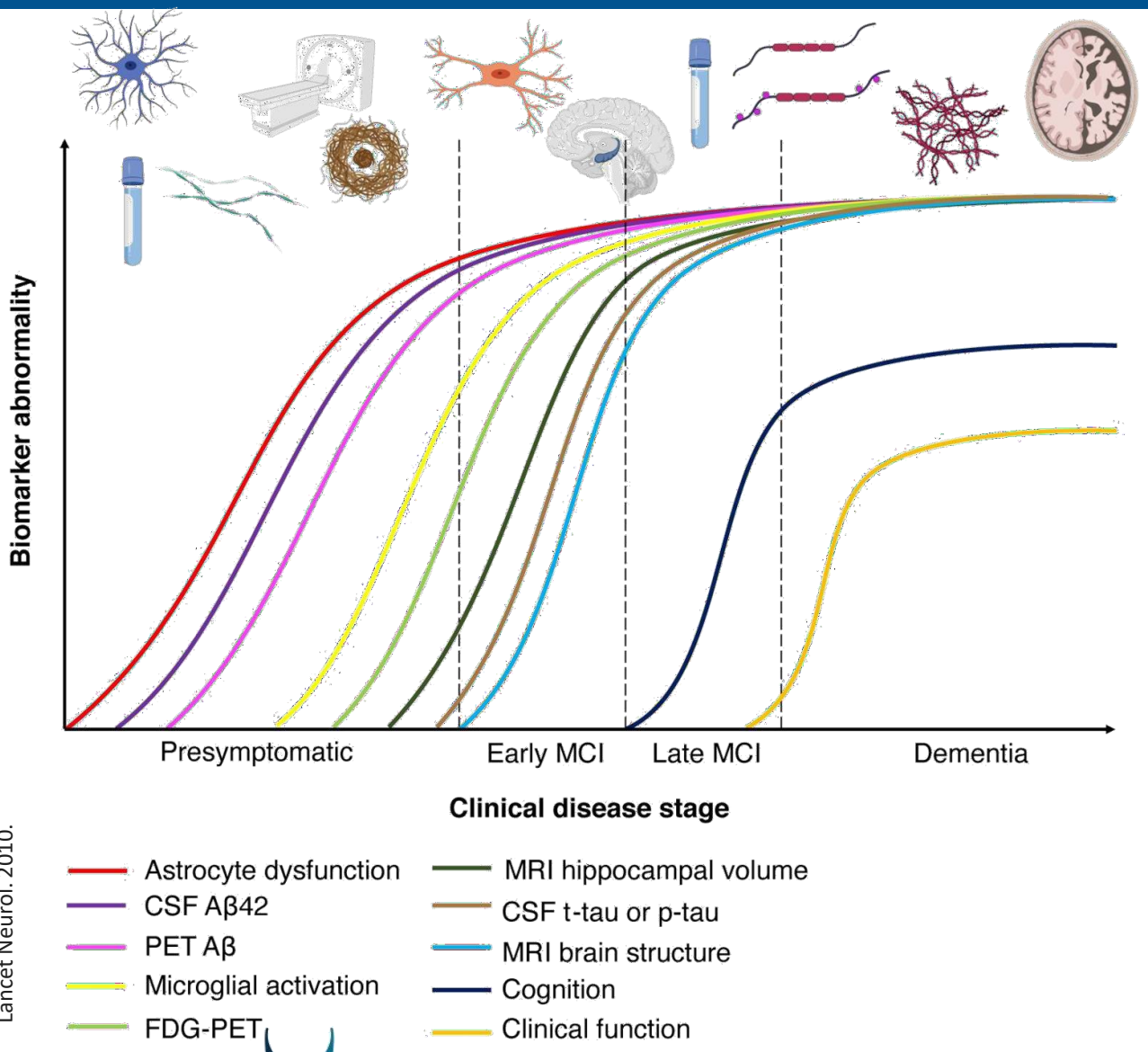
Where do we stand today?

PET/MR special session @ISMRM italian chapter 2024

- Still searching for the killer application
- Technical challenges are almost solved
- PET/MR fostered the virtuous collaboration between NM and MRI communities
- PET/MR is confirming a valuable research tool in Brain Research
- Tool for the study of the relationship of PET and MR imaging markers **(PET is the reference)**
  - SWI/DTI Vs Amyloid-PET
  - GlucoCEST Vs FDG-PET
  - ASLperfusion Vs FDG/earlyAmyloid-PET
- Tool for the study of the relationship among different brain connectivity metrics **(MR is the reference)**

SYNLAB
IRCCS SDN

PM-D Background



Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the **Alzheimer's pathological cascade**. Lancet Neurol. 2010.

TABLE 2. KNOWN PATHOLOGIC FACTORS IN ALZHEIMER'S DISEASE AND RELATED BIOMARKERS

Factor	Imaging	CSF	Blood
Amyloid-β load **A**	[^{11}C]-PIB	Amyloid-β (1-42)	APP 699-711
	[^{18}F]-NAV4694		Amyloid-β (1-42)
	[^{18}F]-florbetapir		Amyloid-β (1-40)
	[^{18}F]-florbetaben		
	[^{18}F]-flutemetamol		
Neurofibrillary tangles **T**	[^{18}F]-Ro948	Phosphorylated tau	The association of serum phosphorylated tau with tangles is unclear
	[^{18}F]-AV1451		
	[^{18}F]-MK6240		
	[^{18}F]-PI2620		
	[^{11}C]-PBBB3		
Neurodegeneration **N**	MRI	Total tau	Neurofilament light chain (NFL)
	[^{18}F]-FDG	Neurofilament light chain (NFL)	
		Neurogranin (Ng)	
		Synaptosomal-associated protein 25 (SNAP-25)	
		Neuron-specific enolase (NSE); heart fatty acid binding protein (HFABP)	
Vascular load	MRI	CSF albumin:plasma albumin ratio	α-synuclein
Lewy body load	N/A	α-synuclein	N/A
Neuroinflammation	Microglial activation:	Microglial activation:	Microglial activation:
	[^{11}C]PK11195	Chitinase-3-like protein 1 (YKL-40)	Chitinase-3-like protein 1 (YKL-40)
	[^{11}C]PBR28	Soluble TREM2 (sTREM2)	Cytokines:
	[^{11}C]DAA1106	Cytokines: TNF-α, IL-6, IL-1β	TNF-α, IL-1 β,
	[^{18}F]DPA714	Chemokines:	Chemokines:
	[^{11}C]DPA713	Monocyte chemotactic protein 1 [MCP-1]	Monocyte chemotactic protein 1
	[^{18}F]ER176		
	[^{18}F]GE180		
	[^{11}C]L-des-deprenyl		

- Dementia requires a multi-modal assessment
- Need for reliable and reproducible (binary) markers

SYNLAB IRCCS SDN

What about«promising» MR techniques in AD?

- QSM (>20 studies) Quantification of iron content, Assessment of myelination, Measuring venous oxygen saturation
  "QSM has the ability to provide pathophysiological information on brain tissue properties and the potential to measure the efficacy of novel therapeutics in clinical settings for AD."
  Studied also In correlation with Amyloid-PET

- DTI (>50 studies) Microstructural assessment ***"Diffusion metrics are associated with cognitive outcomes in AD continuum."***
  Studied also In correlation with Amyloid-PET + CONNECTOMICS

- ASL (>50 studies) ***«Disrupted perfusion is not only evident throughout disease manifestation, it is also demonstrated during the pre-clinical phase of AD"*** but ***" lower sensitivity, specificity and inter-rater reliability for ASL compared to FDG-PET"***

- rs-FMRI (>50 studies) ***«Evidence indicates that the nodes of the DMN can offer moderate to high diagnostic power to distinguish AD and MCI patients."***

SYNLAB IRCCS SDN

RISK: MR protocol can dominate PET/MR examination!

PM-D

Integrated PET/MR scanner as reference imaging tool in the study of dementia: technological and clinical assessment (PM-D) GR-2018-12366779

- Enrollment started late 2020, project results must be delivered in september 2024

AIMS

To evaluate the benefits/costs ratio and feasibility of PET/MR, with respect to standalone PET/CT and MR, in management and diagnosis of dementia patients.

- **PET quantified with and without MR information**

To assess the accuracy of PET/MR biomarkers, and related combinations, to find a reliable clinical protocol.

- **Investigating mutual relationship among imaging markers**

To provide suitable PET/MR imaging protocols, image processing pipelines and structured reports for a comprehensive dementia assessment.

- **Assessing accelerated protocols Vs conventional protocols**

SYNLAB
IRCCS SDN

PM-D: Research design

- Observational cross-sectional prospective study design
- Subjects target: 100 subjects within 55-90 age range

  - **T00 IMAGING:** Amyloid-PET/CT+ structural MRI (MR angiography; volumetric MRI; DT; FLAIR; SWI) with PET coregistration on hybrid PET/MR scanner
  - **T01 IMAGING:** FDG-PET/CT + functional MRI (rs-FMRI, ASL, volumetric T1+T2, T2-FLAIR) with PET coregistration on hybrid PET/MR scanner
  - **Neuropsychological assessment** battery to evaluate long- and short-term memory abilities, frontal/executive functions, visuo-spatial and visuo-constructional abilities

  + Blood Sample

  MR Imaging protocols armonized with Italian Neuroscience Network (RIN)

SYNLAB
IRCCS SDN

Early Amyloid as proxy of Brain Metabolism

Early-Phase ^{18}F-Florbetapir and ^{18}F-Flutemetamol Images as Proxies of Brain Metabolism in a Memory Clinic Setting

Cecilia Boccalini[1–3], Débora Elisa Peretti[1], Federica Ribaldi[4,5], Max Scheffler[6], Sara Stampacchia[1], Szymon Tomczyk[4], Cristelle Rodriguez[7,8], Marie-Louise Montandon[8,9], Sven Haller[10–13], Panteleimon Giannakopoulos[7,8], Giovanni B. Frisoni[4,5], Daniela Perani[2,3,14], and Valentina Garibotto[1,15,16]

J Nucl Med 2023; 64:266–273
DOI: 10.2967/jnumed.122.264256

tively). **Conclusion:** The distribution of perfusion was comparable to that of metabolism at the single-subject level by parametric analysis, particularly in the presence of a high neurodegeneration burden. Our findings indicate that eFBP and eFMM imaging can replace ^{18}F-FDG PET imaging, as they reveal typical neurodegenerative patterns or allow exclusion of the presence of neurodegeneration. The findings show cost-saving capacities of amyloid PET and support routine use of the modality for individual classification in clinical practice.

This is of particular interest in PET/MR:

We could, in principle, envision a «one shop» protocol that dramatically reduce the acquisition time!

SYNLAB IRCCS SDN

During the project we changed the protocol to include also eFMM

Advantages of PET/MR

Today's issues:

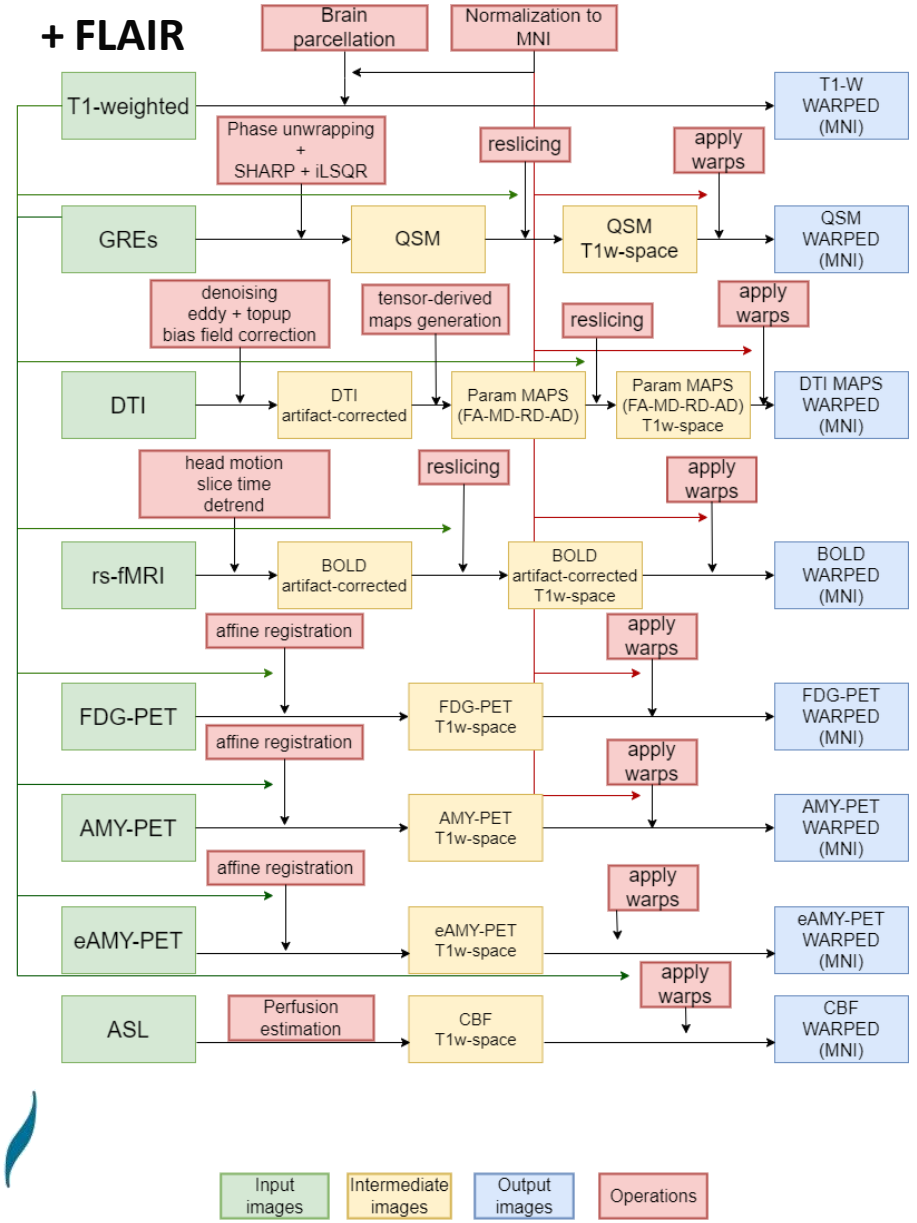
- PET/MR requires one session (and one room)
- MR-driven PET regional quantification works better
- PET/MR examination is shorter than standalone PET + MR

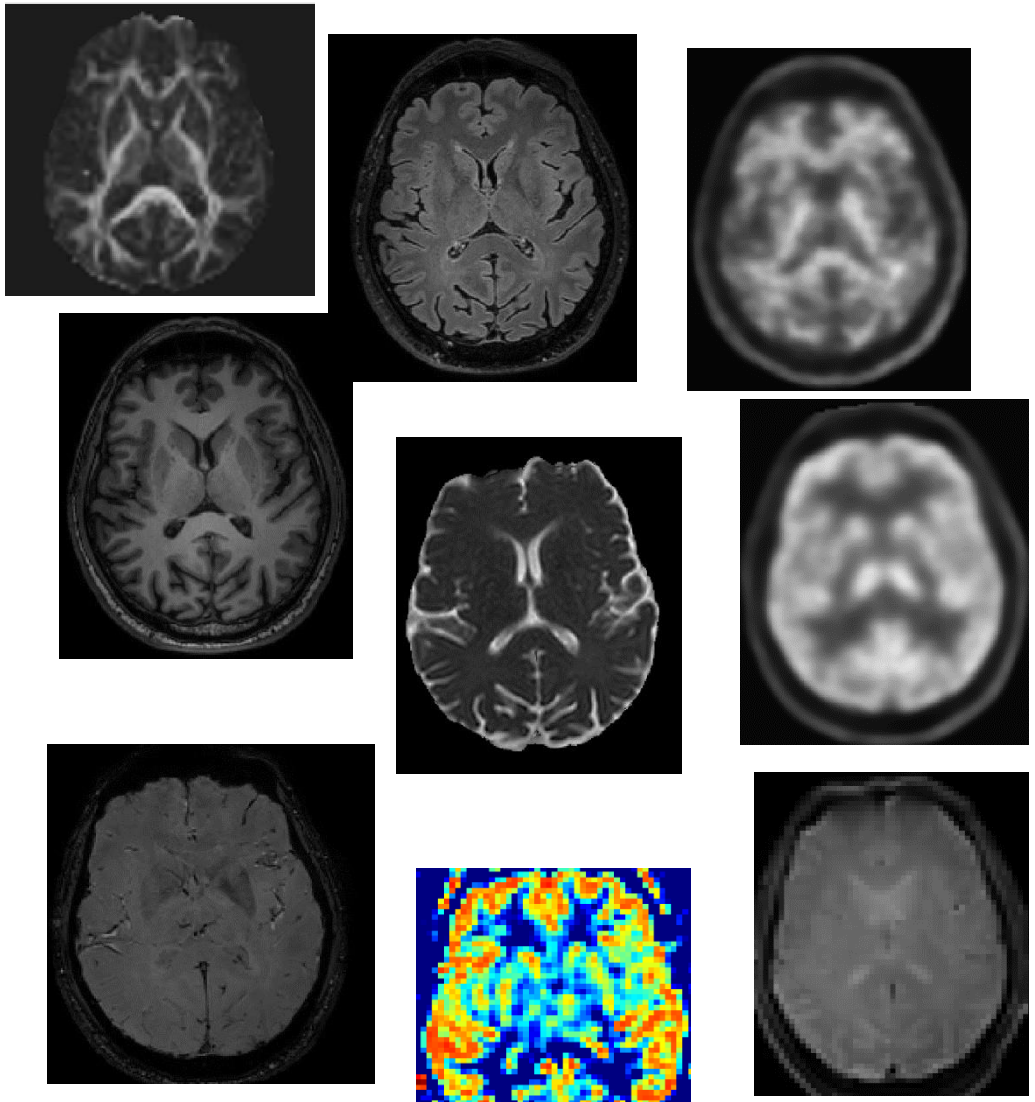
INDIRECT: Can early-amyloid replace FDG-PET in clinical setting?

SYNLAB
IRCCS SDN

PM-D PROCESSING PIPELINE

ACC





TOOLS

- **Freesurfer**
- **LST-LPA**
- **MRtrix**
- **FSL**
- **SPM**
- **AFNI**
- **ANTS**
- **Custom code**

SYNLAB IRCCS SDN

PM-D Sample

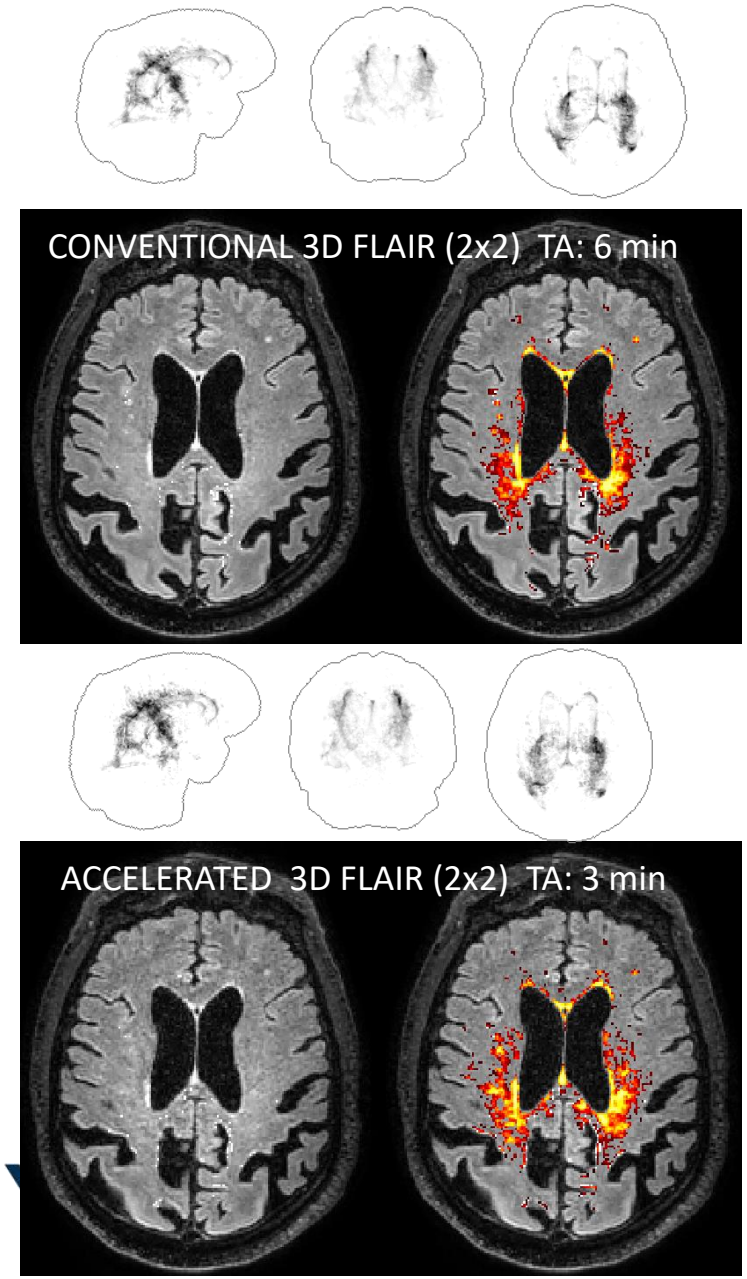
early 2024: 130 subjects

Clinical diagnosis	#
Typical AD (early/late onset)	41
MCI	28
Vascular(Fazekas score >4)/Mixed	25
Atypical AD (executive/behavioural/posterior/logopenic)	21
FTD, PPA, semantic dementia	15

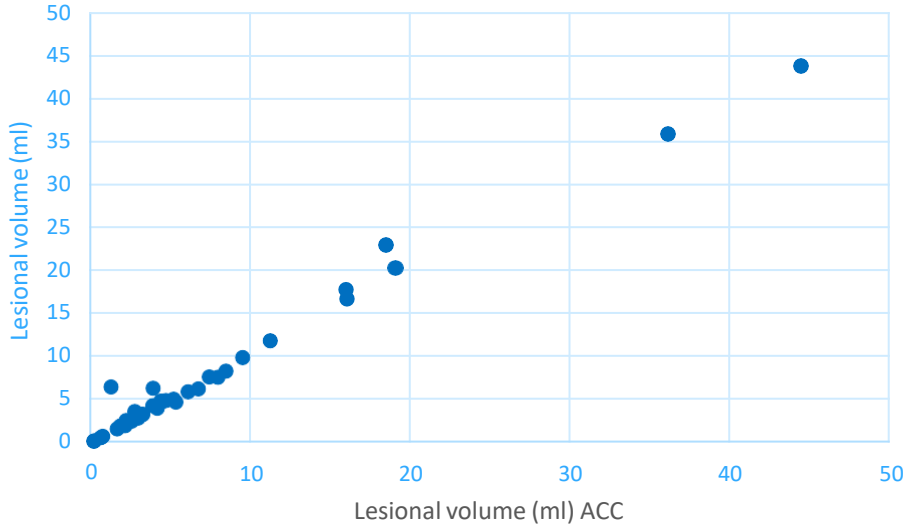
- Age: 65,52 ± 8,36
- AMILOID status: 59 A+
- MMSE: 22,37 ± 6,19
- Gender: 64 F

SYNLAB IRCCS SDN

Accelerated FLAIR

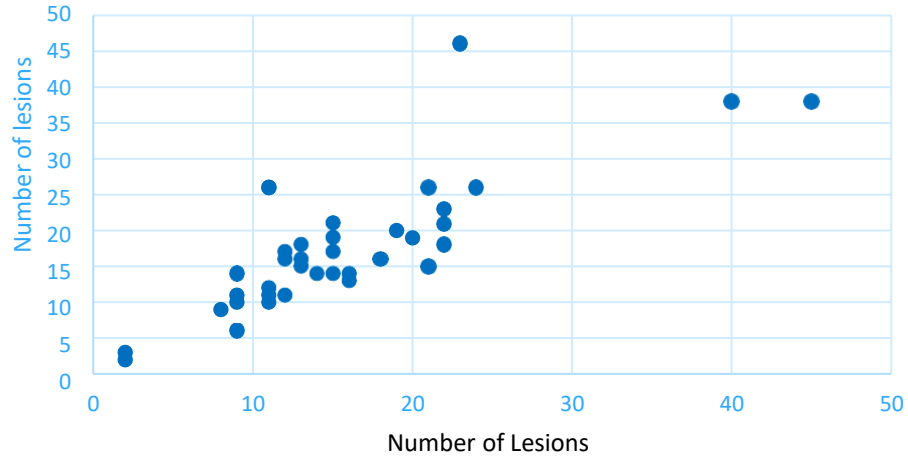


LPA automatic estimation of vascular load

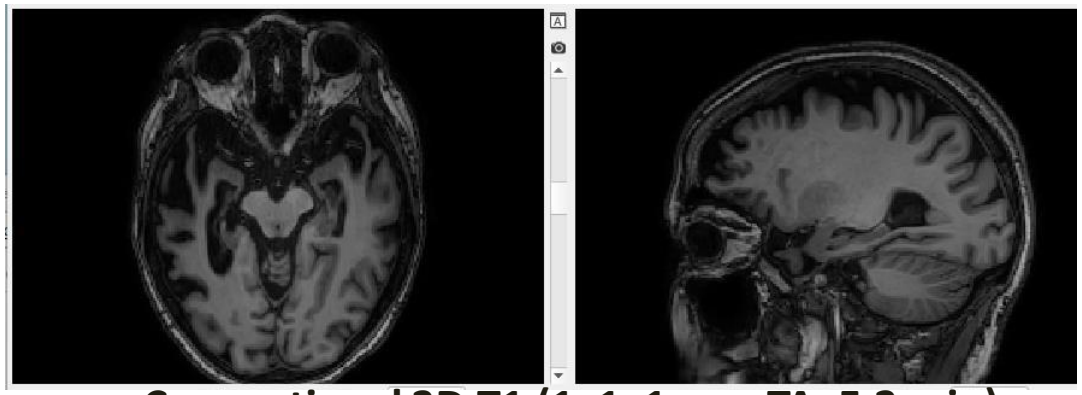


r=0.991

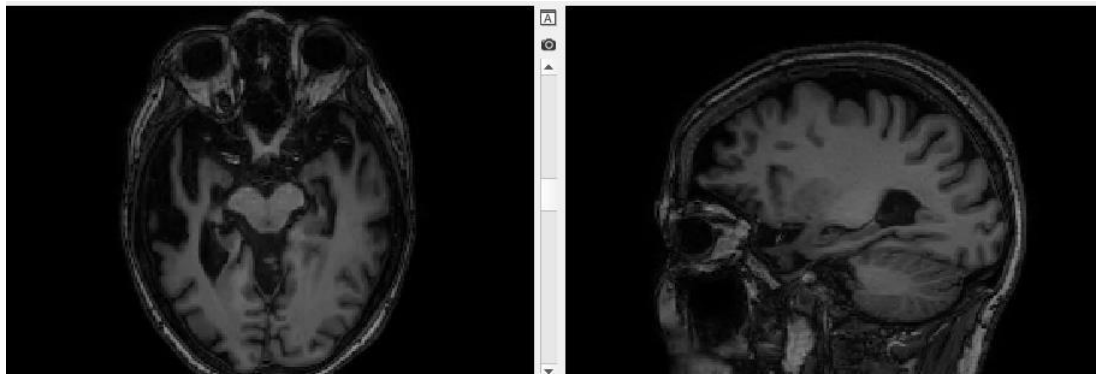
lesions



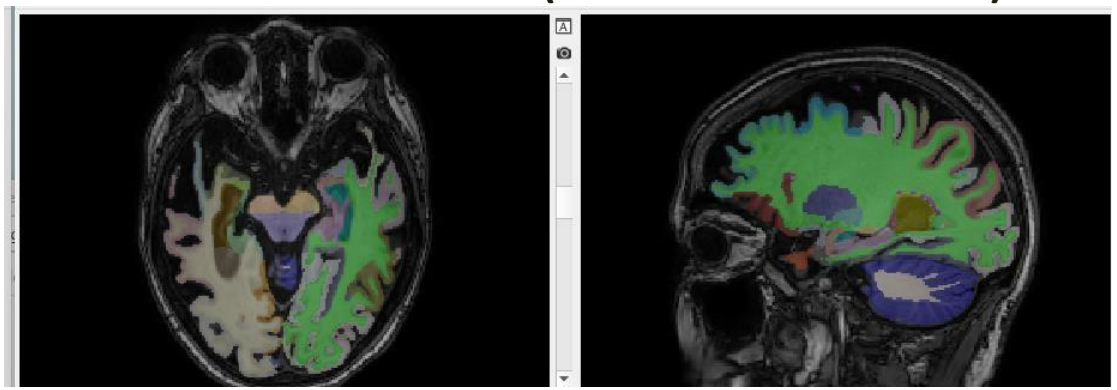
Accelerated Structural T1

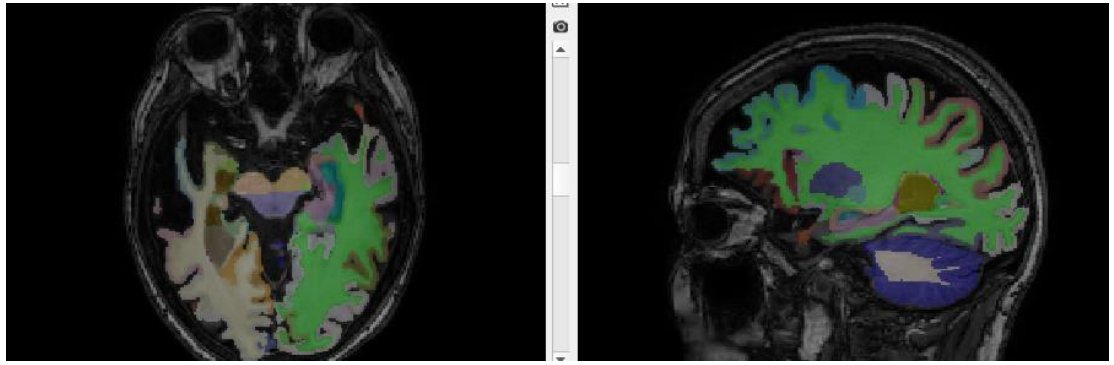


Conventional 3D T1 (1x1x1 mm TA=5.3 min)

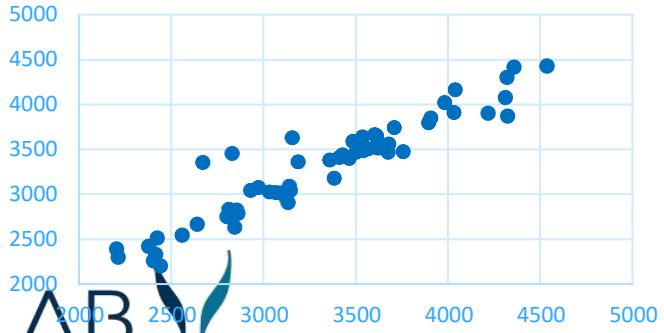


Accelerated 3D T1 (AF: 2x2; 1x1x1 mm TA=2.16 min)



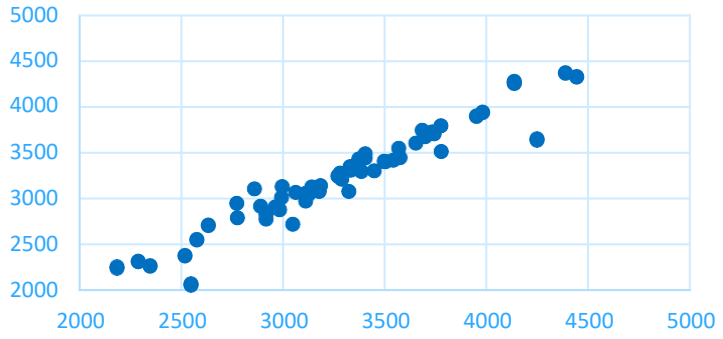


Right-Hippocampus



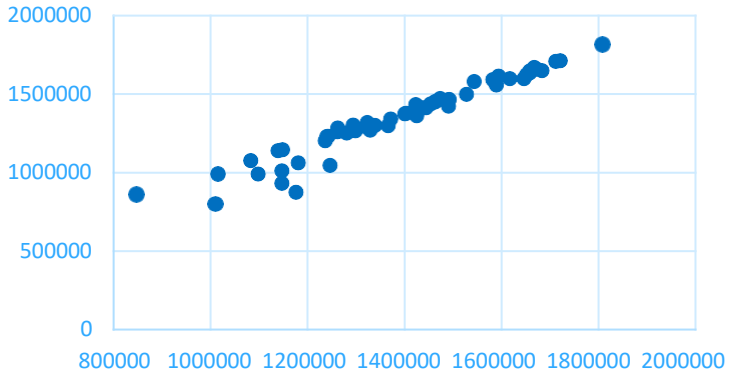
r=0.946

Left-Hippocampus



r=0.963

EstimatedTotalIntraCranialVol



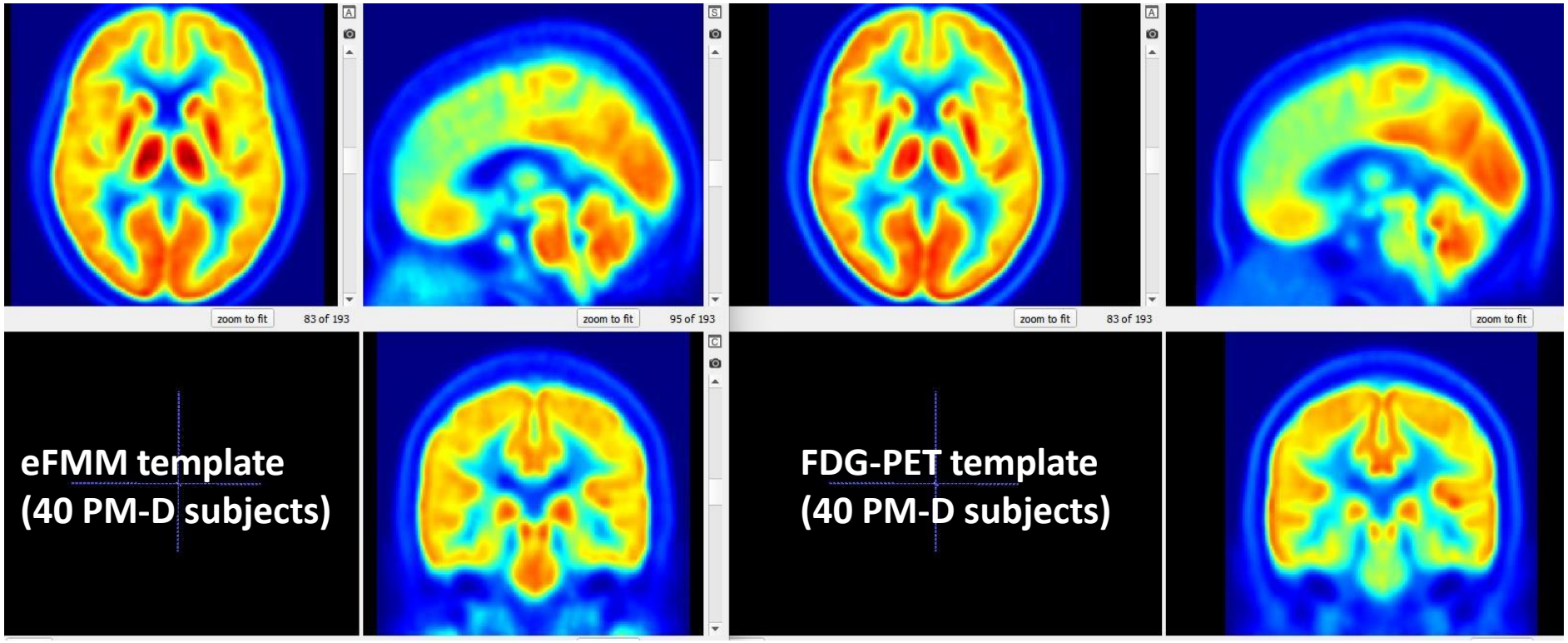
r=0.970

SYNLAB

IRCCS SDN

FDG-PET Vs eFMM

Can early-amiloid replace FDG-PET in clinical setting?

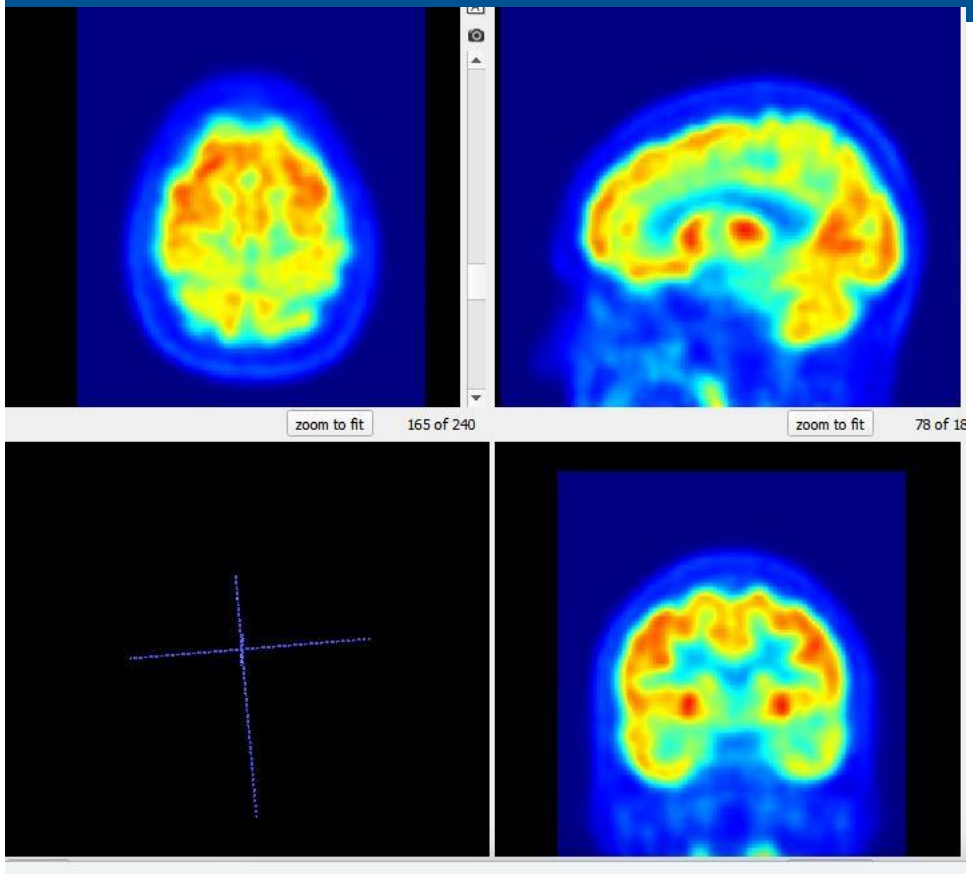


eFMM: early Vizamyl uptake averaged 60'- 480'

SYNLAB IRCCS SDN

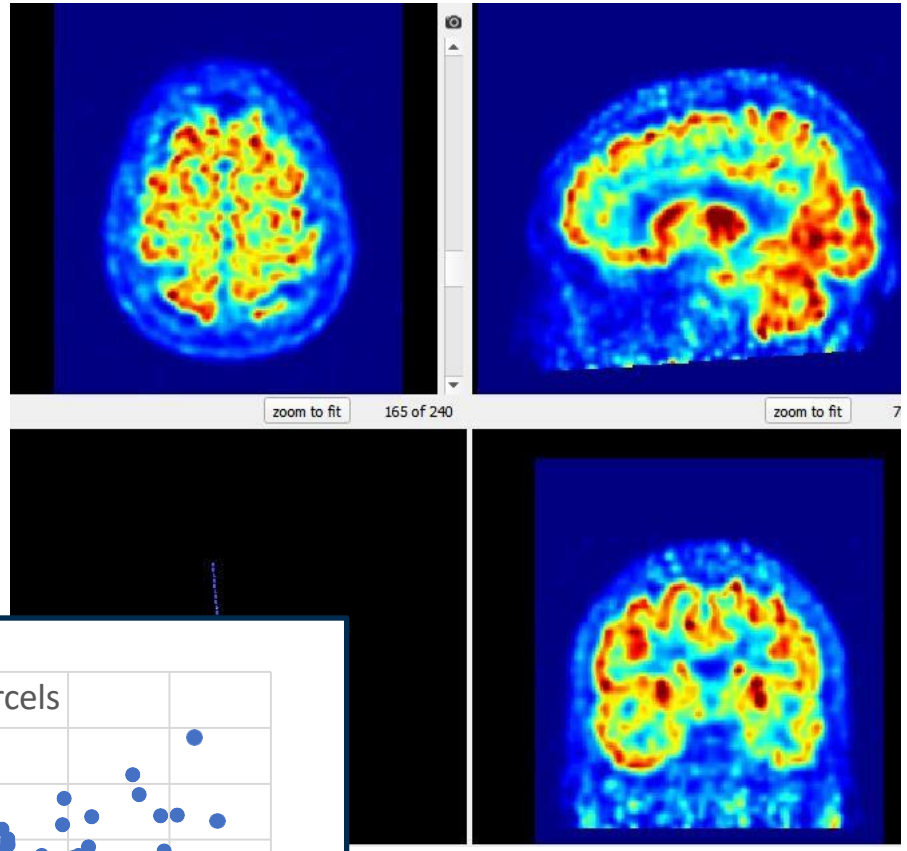
Impressive similarity, major differences in brainstem and thalami

FDG-PET Vs eFMM



FDG-PET

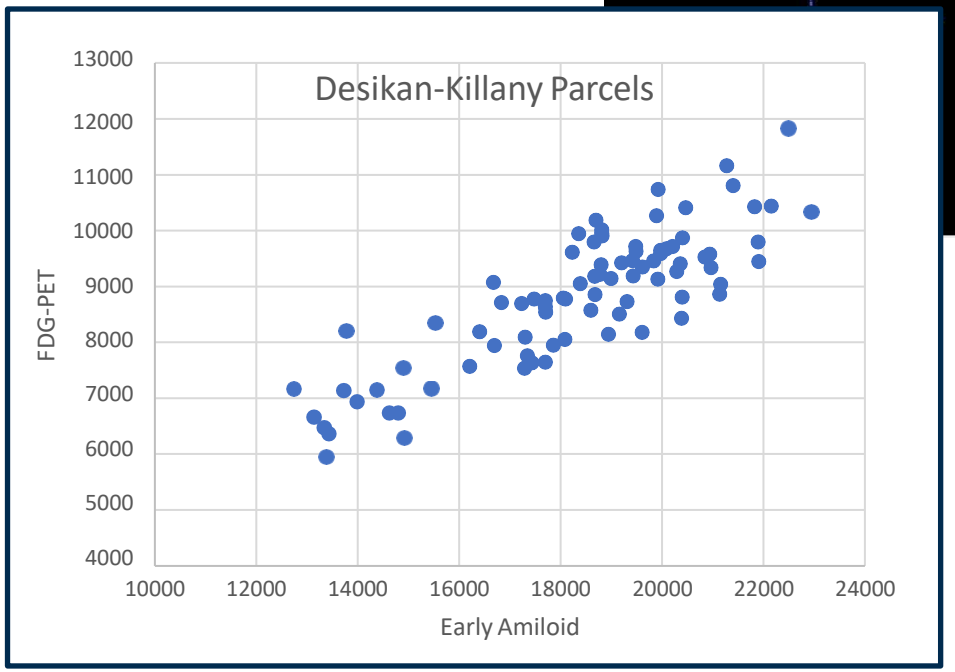
eFMM-PET



60 yo, female

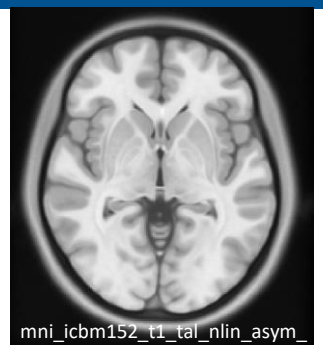
T-P sx and precuneus hypometabolism

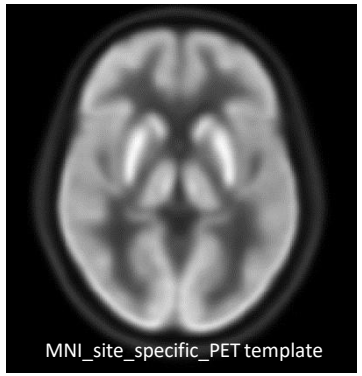
MMSE 28

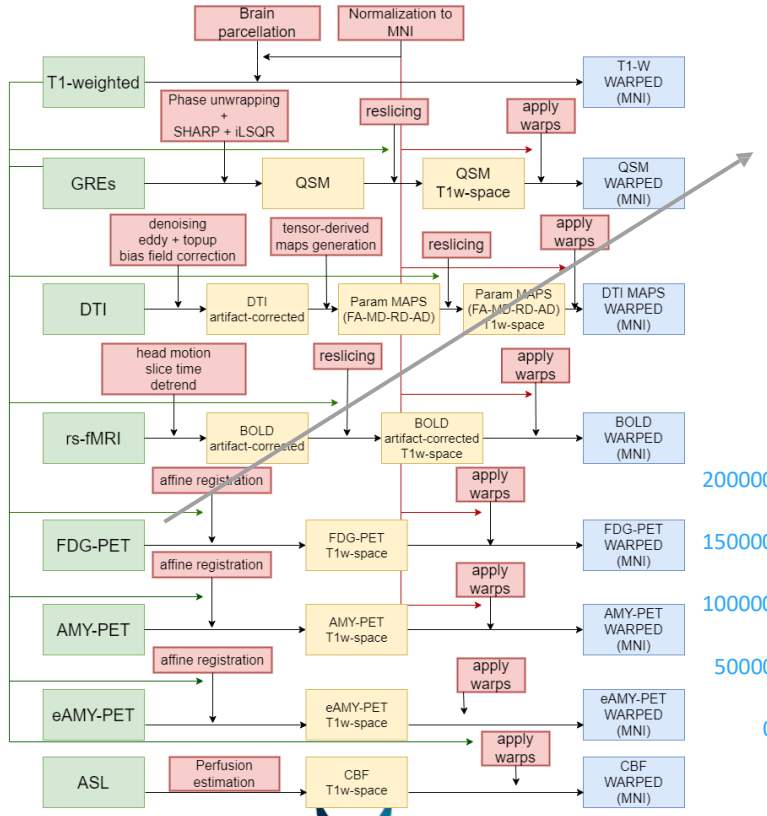


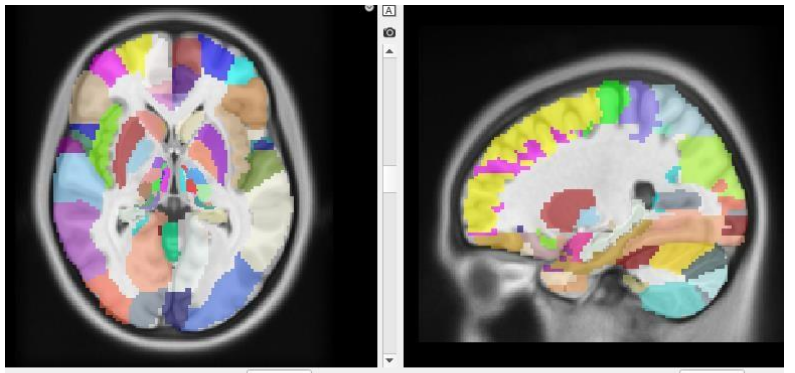
SYNLAB IRCCS SDN

Does MR-driven PET regional quantification work better?

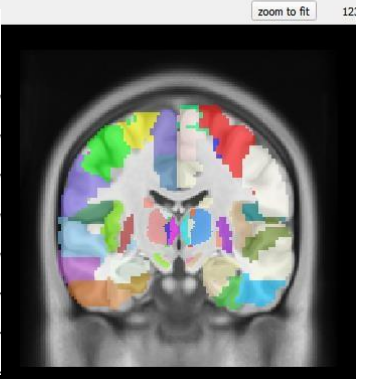






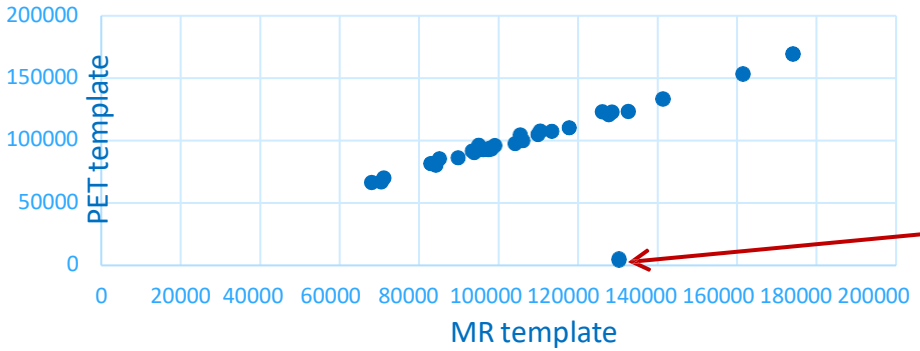


ROI	ROI-weight (%)
Posterior cingulate gyrus	31.238
Fusiform gyrus	15.398
Cuneus	14.148
Medial frontal gyrus	10.524
Globus pallidus	8.848
Angular gyrus	7.499
Sup. parietal lobule	5.693



Rondina et al. Selecting the most relevant brain regions to discriminate Alzheimer's disease patients from healthy controls […]. Neuroimage Clin. 2017

Comparison of PET-driven Vs MRI-driven spatial normalization on AD AAL3 regions (30patients)



Automatic PET normalization failed! 1/30

ANSWER: Not at all, probably MR can be exploited for quantification in native space and PVE estimation

Final remarks

- MR accelerated sequences are reliable for automated softwares (tuned on conventional MR)
- Exploiting early amiloid can deliver comprehensive and clinically feasibile PET/MR protocol for dementia
- Integration with other (bio)markers can play a crucial role for patient's compliace
- A lot of work to do forward:
  - Reprocessing/recovering of PM-D dataset in progress
  - Multivariate statistical framework - evaluation of imaging markers with respect to clinical outcome
  - Role of MR markers to unveil the glucose-perfusion mismatch

SYNLAB
IRCCS SDN

Acknowledgments

Italian MoH project # GR-2018-12366779

RIN Network

rin | rete IRCCS delle neuroscienze e della neuroriabilitazione

PM-D team

Carlo Cavaliere (Radiologist)
Sabina Pappatà (Radiologist)
Vincenzo Alfano (Radiographer)
Pasquale Gisonni (Radiographer)
Angelica de Cecca (Neuropsycologist)
Emanuele Nicolai (NM physician)
Elena Salvatore (Neurologist)
Rosa Iodice (Neurologist)
Marco Salvatore (Scientific Director)

SYNLAB
IRCCS SDN

Acknowledgments

Italian MoH project # GR-2018-12366779

RIN Network

rin | rete IRCCS delle neuroscienze e della neuroriabilitazione

PM-D team

Carlo Cavaliere (Radiologist)
Sabina Pappatà (Radiologist)
Vincenzo Alfano (Radiographer)
Pasquale Gisonni (Radiographer)
Angelica de Cecca (Neuropsycologist)
Emanuele Nicolai (NM physician)
Elena Salvatore (Neurologist)
Rosa Iodice (Neurologist)
Marco Salvatore (Scientific Director)

Thank You!

SYNLAB IRCCS SDN

Backup slide 1: PM-D Background

- **2013-2024 PET/MRI exploited as research tool**

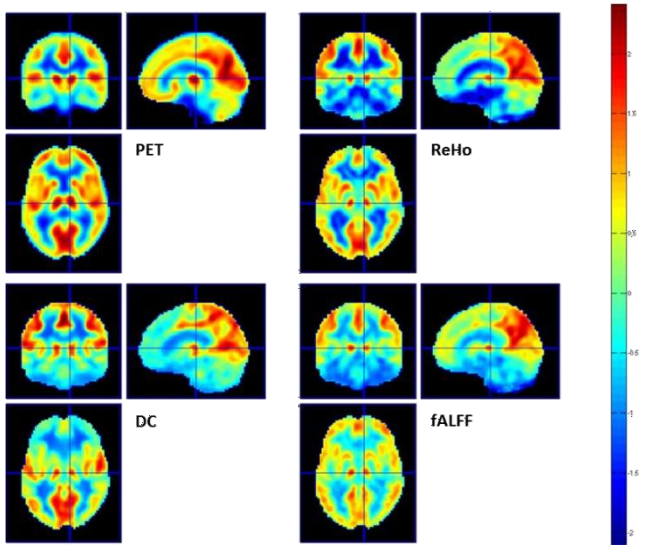
2015 Aiello M, Salvatore E, Cachia A, Pappatà S, Cavaliere C, Prinster A, Nicolai E, Salvatore M, Baron JC, Quarantelli M. Relationship between simultaneously acquired resting-state regional cerebral glucose metabolism and functional MRI: a PET/MR hybrid scanner study. Neuroimage. 2015

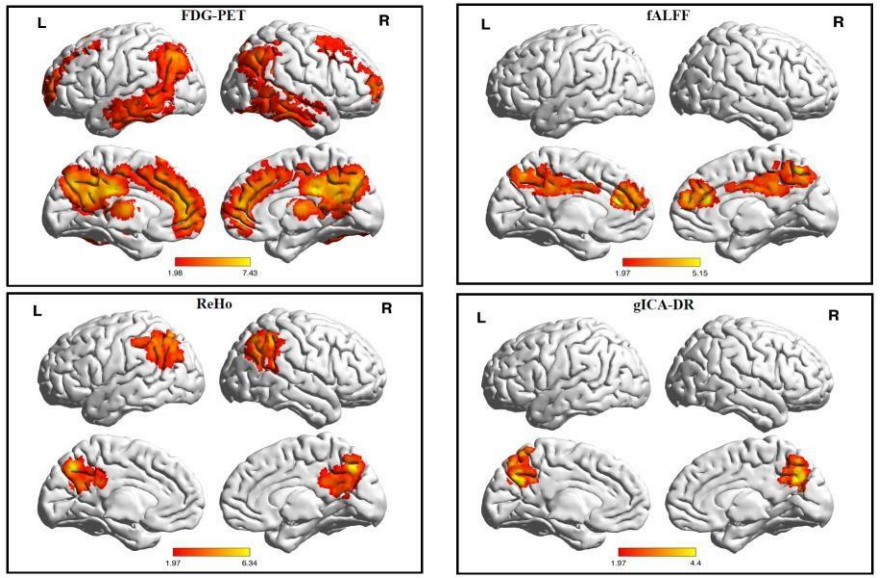
2016 Aiello, M., Cavaliere, C., & Salvatore, M. (2016). Hybrid PET/MR imaging and brain connectivity. *Frontiers in neuroscience*, *10*

2018 Aiello M, Marchitelli R, Cachia A, Quarantelli M, Cavaliere C, Postiglione A, Tedeschi G, Montella P, Milan G, Salvatore M, Salvatore E, Baron JC, Pappatà S. Simultaneous resting-state FDG-PET/fMRI in Alzheimer Disease: Relationship between glucose metabolism and intrinsic activity. Neuroimage. 2018

2022 Palombit A, Silvestri E, Volpi T, Aiello M, Cecchin D, Bertoldo A, Corbetta M. Variability of regional glucose metabolism and the topology of functional networks in the human brain. Neuroimage. 2022

2024 Volpi, Silvestri, Aiello, Lee, Vlassenko, Goyal, Corbetta, Bertoldo. The brain's "dark energy" puzzle: how strongly is glucose metabolism linked to resting-state brain activity? JCBFM, 2024

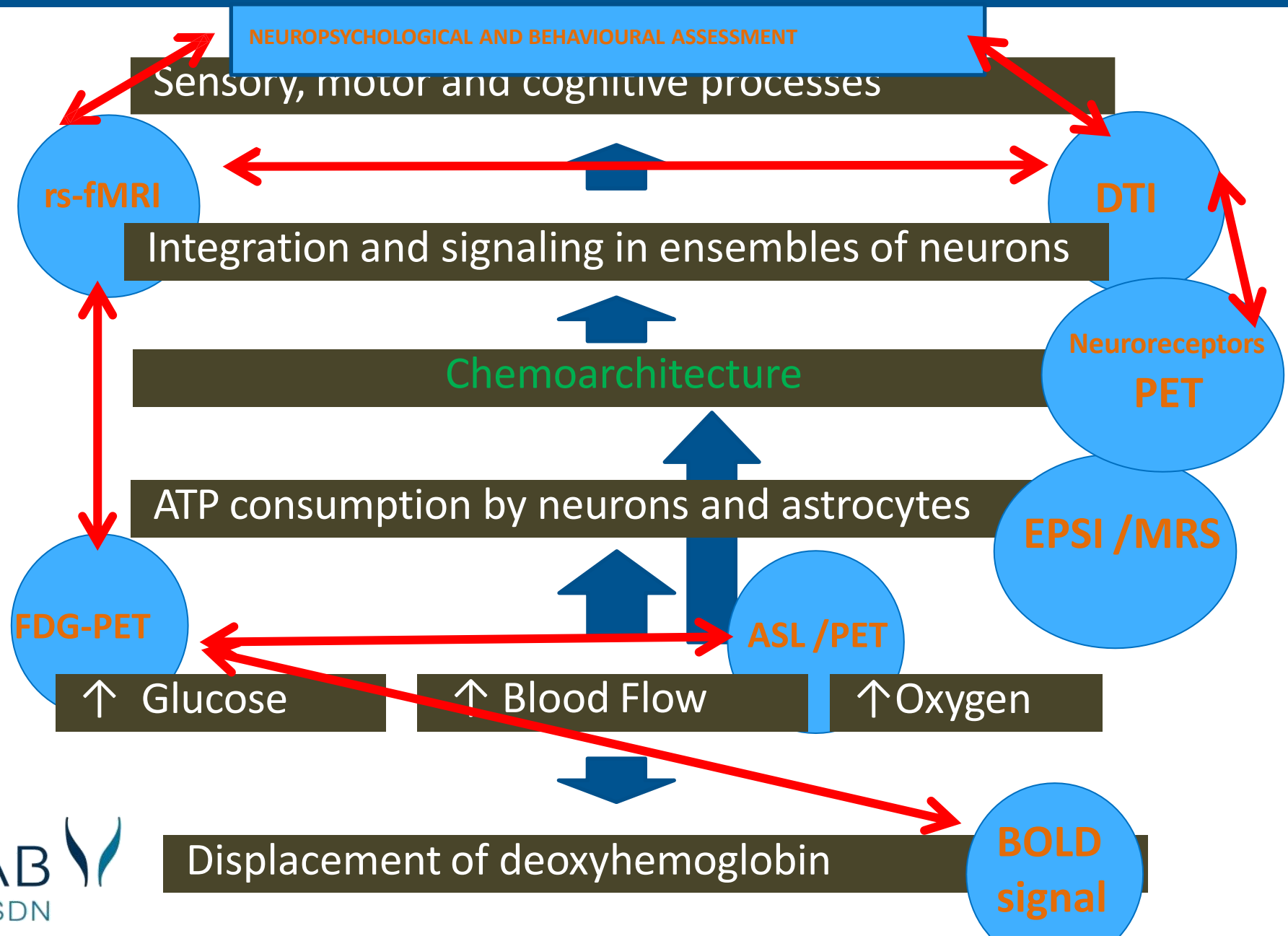




SYNLAB IRCCS SDN

Università degli Studi di Padova

Backup slide 2 - PM-D Background: Multimodal Window on the Brain



SYNLAB IRCCS SDN

Backup slide 3: PM-D Background

TABLE 1. AMYLOID-TAU-NEURODEGENERATION CLASSIFICATIONS FOR ALZHEIMER'S DISEASE	
NIA-AA Research Framework	
Amyloid (A)	Cerebrospinal fluid Aβ42, or Aβ42/Aβ40 ratio
	Amyloid-positron emission tomography
Tau (T)	Cerebrospinal fluid phosphorylated-tau
	Tau positron emission tomography
Neuro-degener-ation (N)	Anatomic MRI
	Fluorodeoxyglucose-positron emission tomography
	Cerebrospinal fluid total tau
Clinical Linkages for Individuals With Symptoms	
$A^+T^+N^-$	Prodromal Alzheimher's disease/mild cognitive impairment due to Alzheimer's disease
$A^+T^+N^+$	Alzheimer's disease dementia (can still be mixed dementia)
$A^-T^+N^-$	Cerebrovascular disease, prion disease, early tauopathies
$A^-T^+N^+$	Vascular dementia, tauopathies, dementia with Lewy bodies, primary age-related tauopathy
$A^-T^-N^+$	Limbic-predominant age-related TDP-43 encepha-lopathy

Biomarker category	fluid	imaging
Core Biomarkers		
A (Ab proteinopathy)	Ab42/40	Amyloid PET
T (AD tau proteinopathy)	ptau 181, 217	Tau PET
Non - specific biomarkers of tissue reaction involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co-pathology		
V vascular brain injury		Anatomic infarction, WMH, abundant dilated perivascular spaces
S α-synuclein	αSyn-SAA*	

SYNLAB IRCCS SDN

practicalneurology.com/articles/2019-june/alzheimers-disease-biomarkers

Backup slide 4: RIN NETWORK

rete IRCCS delle neuroscienze e della neuroriabilitazione

Harmonized MR protocol comparable with PM-D (NO ASL, NO PET)

	CN	AD	DLB	FTD	P-value
N°	118	106	27	46	-
Gender (M/F)	46 / 72	43 / 63	21 / 6	35 / 11	-
Age (y)	64.54 ± 8.67	71.5 ± 7.1	74.37 ± 6.1	69.00 ± 7.3	**<0.001**
Education (y)	13.63 ± 4.93	10.5 ± 4.8	10 ± 4.0	10.3 ± 4.5	**<0.001**
MMSE	-	23.4 ± 4.1	24.8 ± 3.9	23.1 ± 3.9	N.S.
CDR	-	0.5 (51) 1 (48) >1 (3)	0.5 (9) 1 (13) >1 (1)	0.5 (24) 1 (16) >1 (6)	N.S.
NPI	-	13.9 ± 12.6	14.8 ± 10.6	18.2 ± 16.2	N.S.
FAB	-	12.2 ± 3.6	10.3 ± 5.2	11.1 ± 3.7	N.S.
TMT-A	-	100.2 ± 102.8	117.7 ± 149.5	72.9 ± 59.8	N.S.
TMT-B	-	216.4 ± 162.1	192.1 ± 146.4	196.1 ± 114.5	N.S.
Subtypes	-	80% typical AD 8% atypical AD 6% PCA 6% mixed AD	-	63% bhv FTD 7% non-fluent/agram PPA 17% Semantic PPA 13% logopenic non-AD PPA	-

***Table 1**: RIN group characteristics*

Table 1
Demographic and MR scanner details of the multi-centric study.

Site	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (#)	31.8 ± 1.8 (3)	29.6 ± 2.7 (5)	29.7 ± 4.3 (6)	26.3 ± 5.9 (6)	28.0 ± 2.3 (5)	30.0 ± 4.4 (5)	32.2 ± 3.0 (5)	31.8 ± 5.2 (5)	25.0 ± 2.0 (3)	31.6 ± 6.3 (5)	25.1 ± 3.3 (7)	29.2 ± 3.0 (5)	28.5 ± 5.6 (4)
Gender (F/M)	1/2	4/1	5/1	4/2	1/4	3/2	3/2	3/2	1/2	4/1	6/1	2/3	2/2
MRI vendor	V1	V2	V1	V3	V3	V2	V3	V1	V1	V1	V3	V3	V2
RF head-coil	SENSE-Head-32	SENSE-Head-32	SENSE-Head-32	Head-Neck 64	HeadMatrix-4	HNS (8ch)	SENSE-Head-32	SENSE-Head-32	SENSE-Head-32	SENSE-Head-32	Head-Neck 64	Head-Neck 16	Head-Neck 32

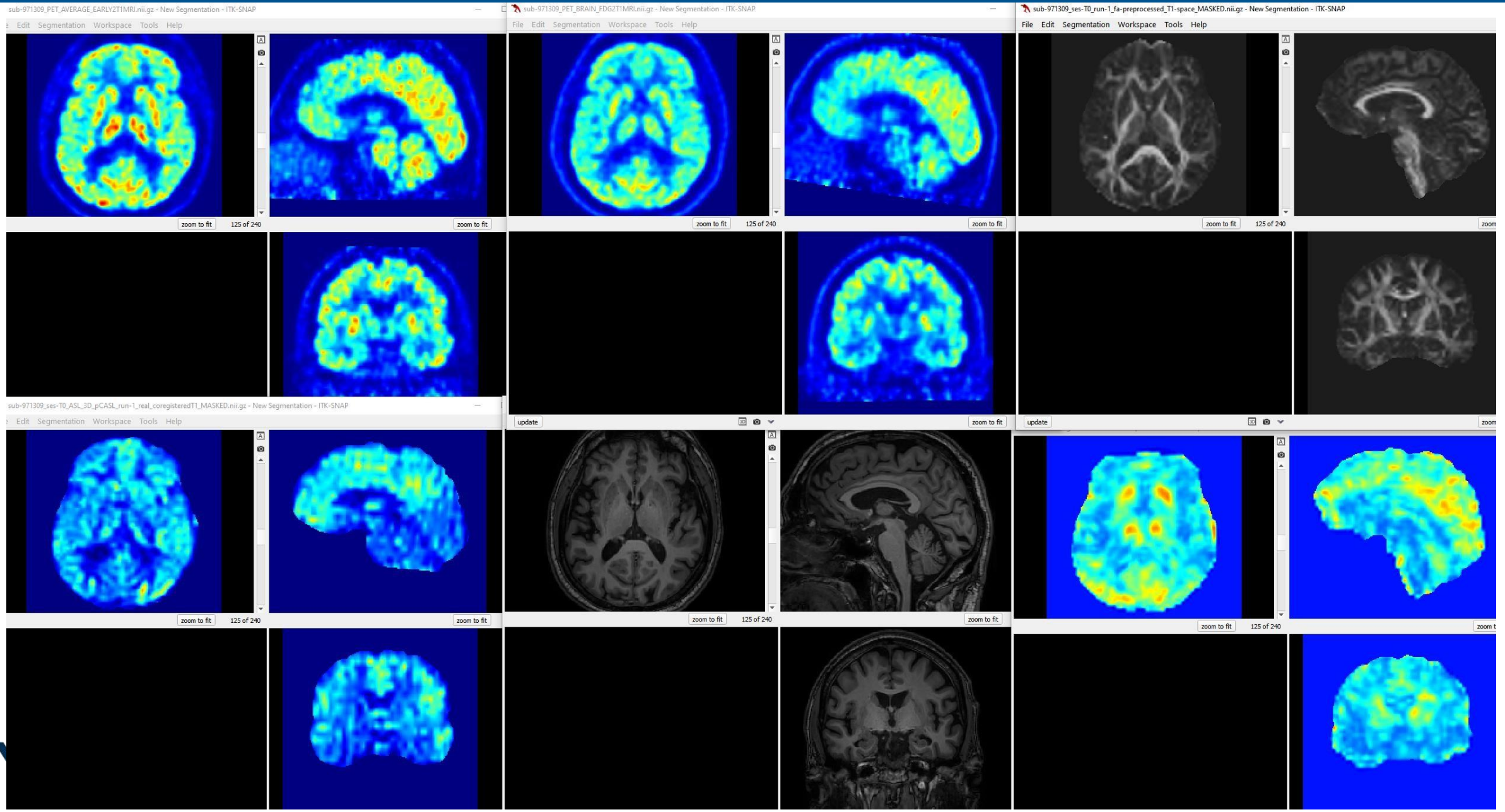
SYNLAB IRCCS SDN

Pasquale Borrelli, Giovanni Savini, Carlo Cavaliere,……., Michela Tosetti, Marco Salvatore, Claudia A.M. Gandini Wheeler-Kingshott, Marco Aiello, Normative values of the topological metrics of the structural connectome: A multi-site reproducibility study across the Italian Neuroscience network, Physica Medica, Volume 112, 2023.

Backup slide: PET/MR Imaging markers of dementia

Marker	Modality	Metric	Acquisition time (approx)	Acceleration	Clinical marker
Atrophy patterns	T1-w	GCA scale / MTA scale Koedam score	6’	3	Y
Anatomical simmetry	T1-w		‘’		
Pathological hallmark	Amyloid-PET Tau-PET	BAPL score,….	10’		Y
Microstructural alterations	DT	FA, RD, AD	7’	3.5’	
Structural connectivity	DT	Graph metrics	‘’	x	
Functional connectivity	rs-fMRI	GoF/ Graph metrics	7’	x	
Abnormal myelination/ leukoaraiosis	T2-w FLAIR	Fazekas	6’	3	Y
Neuronal metabolism	FDG-PET	PALZ,…	10’		Y
Brain perfusion	ASL	Regional CBF	6’	x	
Cerebral microbleeds	SWI	MARS	6’		
TOTAL			56’	43’	

Backup slide 5: eFMM,FDG,FA,CBF,T1w,ReHo



Backup slide 6: HTA

1) The technology must have final approval from the appropriate governmental regulatory bodies (e.g. FDA).
2) The scientific evidence must permit conclusions concerning the effectiveness of the technology on health outcomes.
3) Compare the effectiveness of the technology with that of established technologies.
4) The technology must improve the net health outcome.
5) The technology must be as beneficial as any established alternatives.
6) The improvement must be attainable outside the investigational settings.
7) Summarize the scientific evidence that supports the fiscal impacts of the technology to the target population.
8) Which hospitals currently offer this technology and/or payers reimburse for use of this technology?
9) List and describe relevant, published evidence based guidelines on this technology?

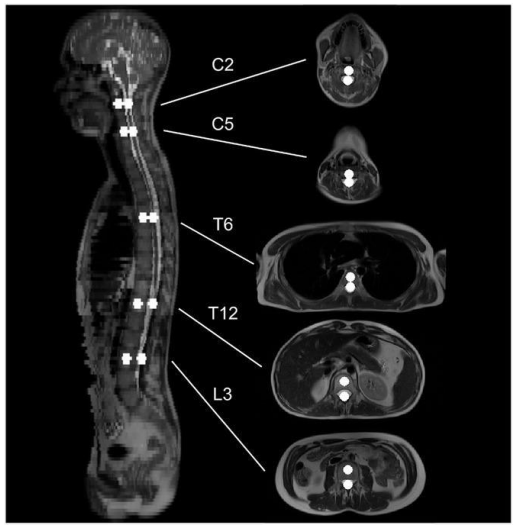
Landaas, E., Devlin, A., Walerius, E., Buckingham, S., Flum, D., Pellegrini, C., . . . Sullivan, S. (2018). OP101 Hospital-Based Health Technology Assessment At UW Medicine. *International Journal of Technology Assessment in Health Care*

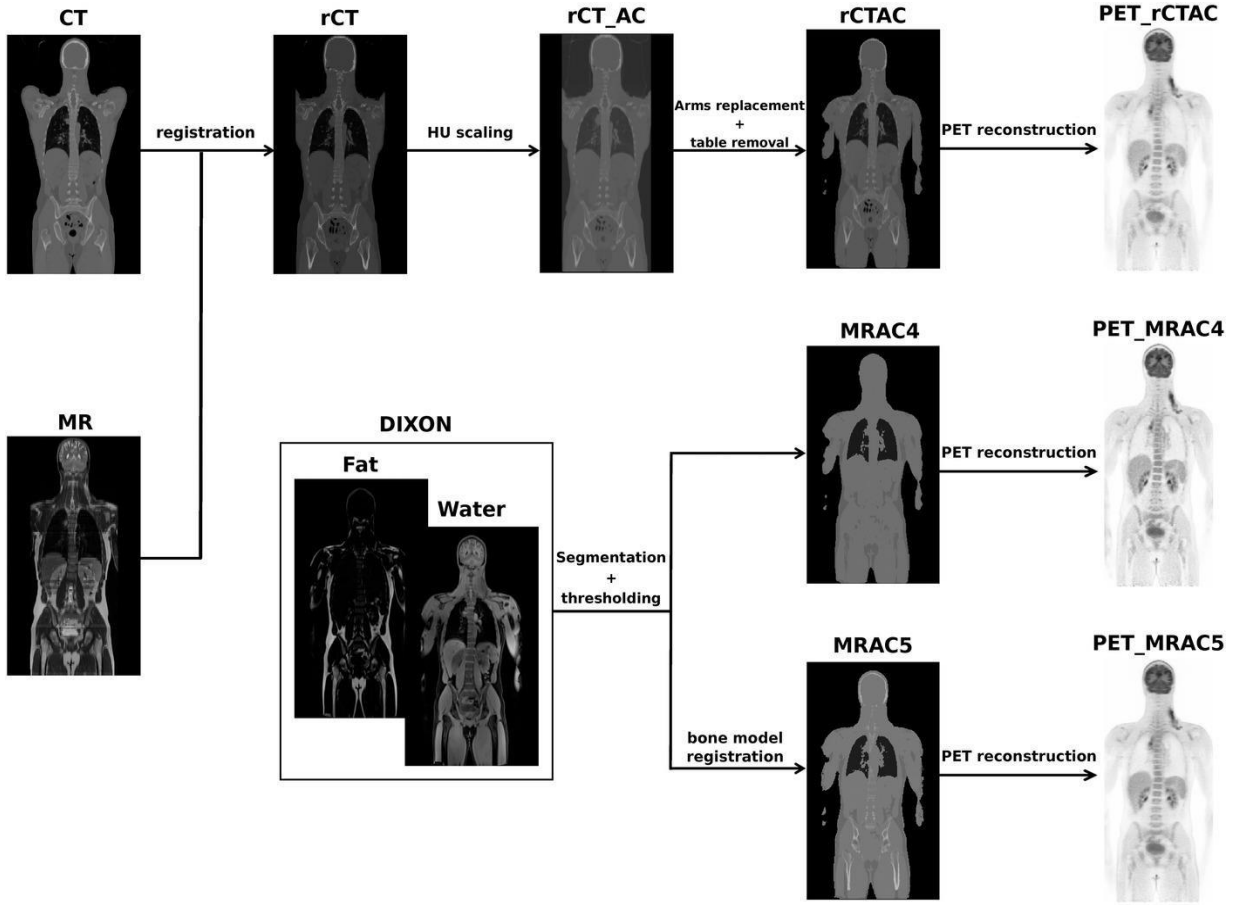
SYNLAB IRCCS SDN

PM-D project includes specific surveys and activities to quantitatively answer

Backup slide 7: Looking Forward: from the brain to the spinal cord

Preliminary works to establish the feasibility and normative values of spinal cord PET/MRI for neurological diseases





Brancato V, Borrelli P, Alfano V, Picardi M, Mascalchi M, Nicolai E, Salvatore M, Aiello M. The impact of MR-based attenuation correction in spinal cord FDG-PET/MR imaging for neurological studies. Medical Physics, 2021

Aiello, M., Alfano, V., Salvatore, E., Cavaliere, C., Picardi, M., Della Pepa, R., ... & Mascalchi, M. (2020). [18 F] FDG uptake of the normal spinal cord in PET/MR imaging: comparison with PET/CT imaging. *EJNMMI research*, *10*(1), 1-9.

SYNLAB IRCCS SDN

Backup slide 8: Killer Application?

PSMR 2012

Scientific Programme

Keynote Speaker

Bernd Pichler, Germany, *The search for the killer application in PET-MR*

"killer applications" – i.e., applications where PET/MRI would yield a significant clinical benefit, in comparison with the most widely established hybrid imaging technique, PET/CT (PET/computed tomography), or in comparison with MRI – has been a major topic of discussion in the radiology and nuclear medicine communities alike.

SYNLAB
IRCCS SDN

Backup slide 9: A detail of T1 acc Vs conventional