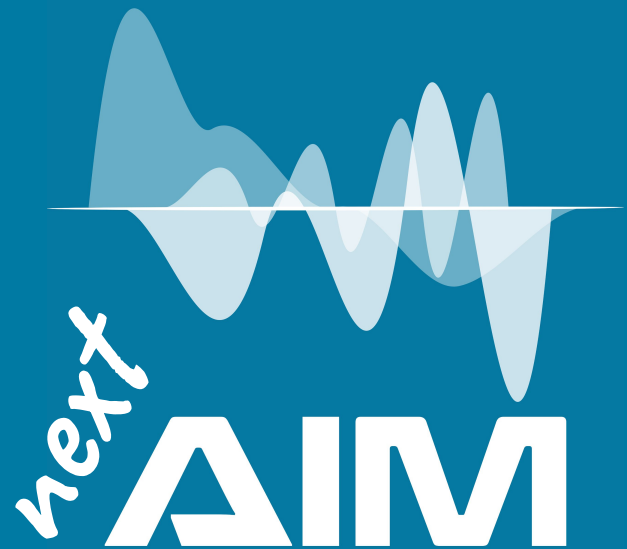


# Artificial Intelligence in Medicine



## Nuclear Medicine Neuroimaging Quantification

Enrico Peira

next\_AIM general meeting

14.02.2023, Milano



DORIAN  
evolving neuroimaging



# Diagnosis ORiented ANalysis (DORIAN)



DORIAN delivers a fast and reliable tool for the **quantification** of medical imaging to support the early and differential diagnosis of neurodegenerative disorders. It provides clinicians and researchers with state-of-the-art robust, rater-independent and reproducible quantitative biomarkers to **better evaluate** dementias stage and progression, **complementing** their ability to write informed medical reports and improve on the early detection and diagnosis of neurodegenerative diseases.

## Dorian recent activity

- > Fondazione spin-off
- > Lab sessions @ Nucl. Med. school in Neurology
- > EBAN finalist
- > Unicredit StartLab 3rd classified
  - >> Amazon AWS academy invitation
- > Lab sessions @ Nucl. Med. school in Neurology

[May 2020]

[Sep. 2021]

[Mar.2022]

[May 2022]

[Sep. 2022]

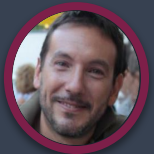
[Oct. 2022]

A. Chincarini  
(INFN-GE)



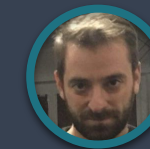
P. Bosco  
(IRCCS Stella Maris, Pisa)

M. Corosu  
(INFN-GE)

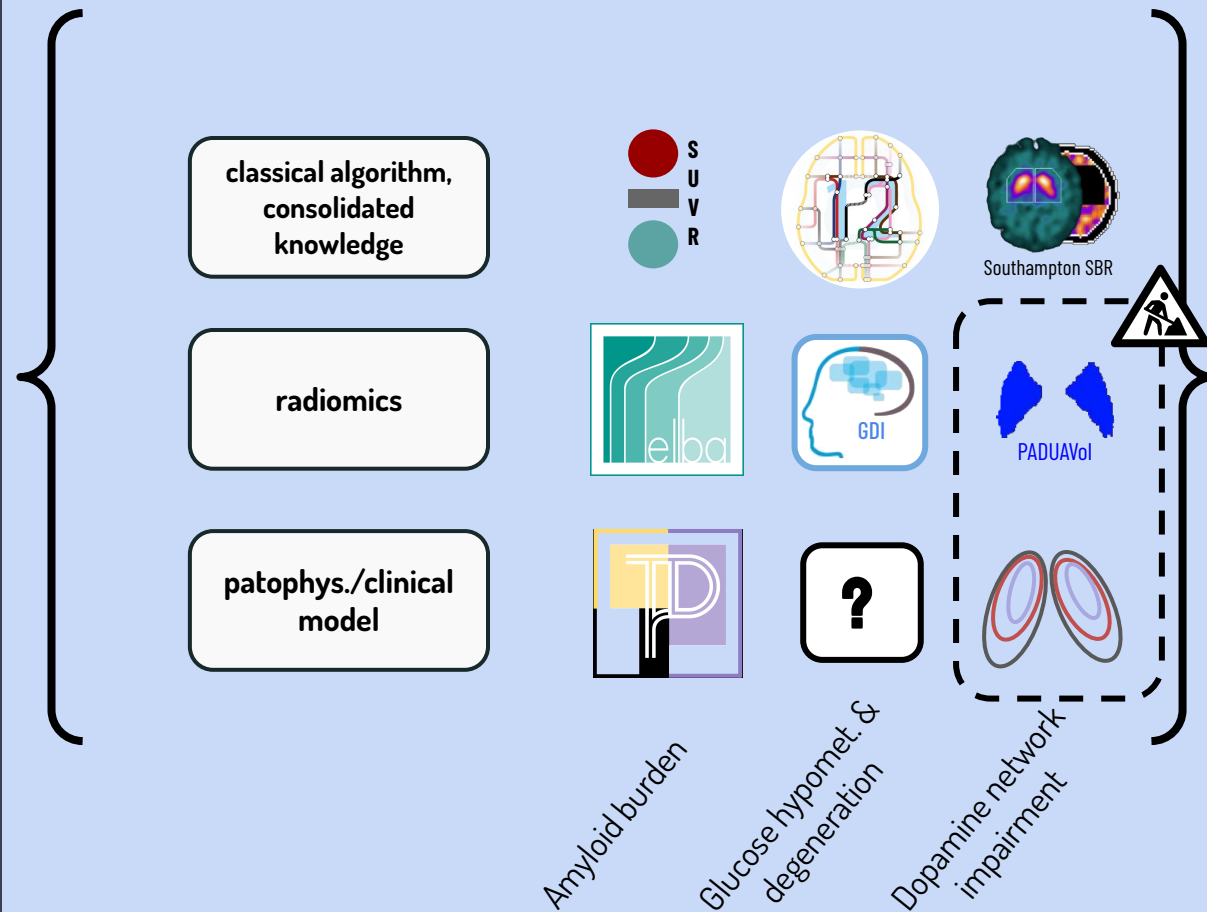


E. Peira  
(INFN-GE)

R. Gianeri  
(INFN-GE)



F. Sensi  
(IRCCS San Martino,  
Genova)



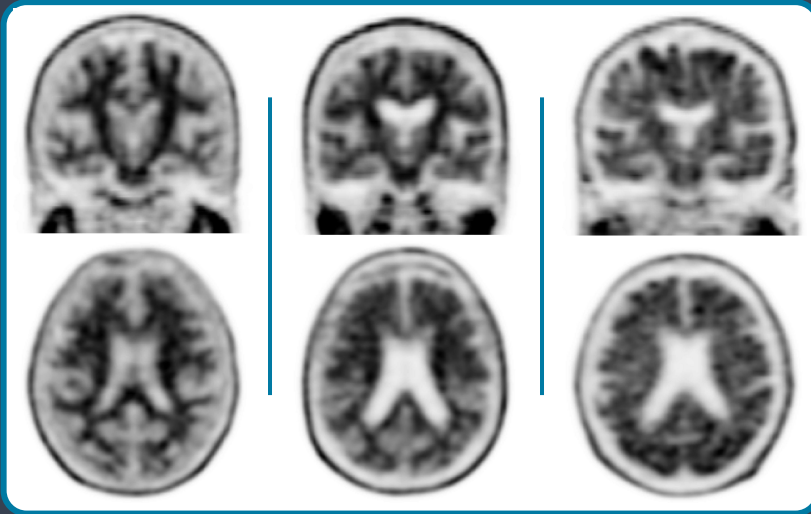
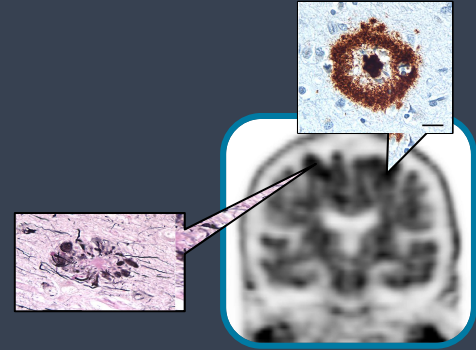


# AMYLOID BURDEN



# What is amyloid PET?

- **In-vivo** assessment of  **$\beta$ -amyloid** in brain tissue
- **A $\beta$**  plaques: pathological hallmark of Alzheimer's disease
- In clinical practice the amy-PET is visually inspected (**binary classification**)



n

?

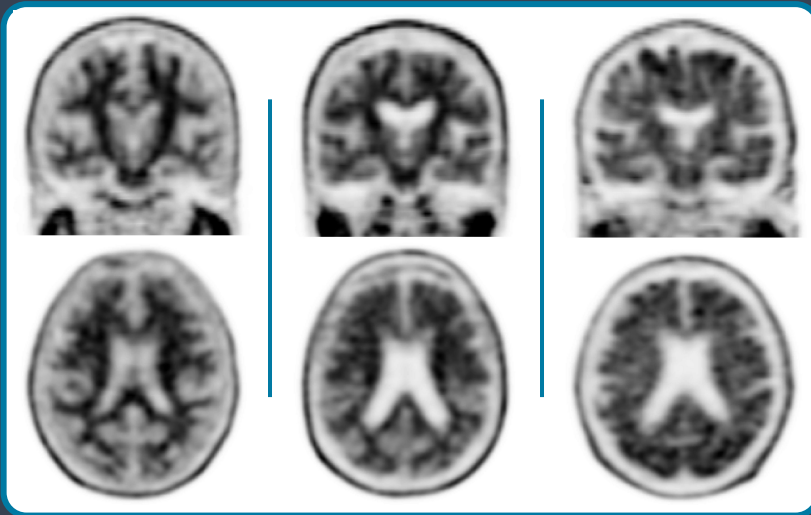
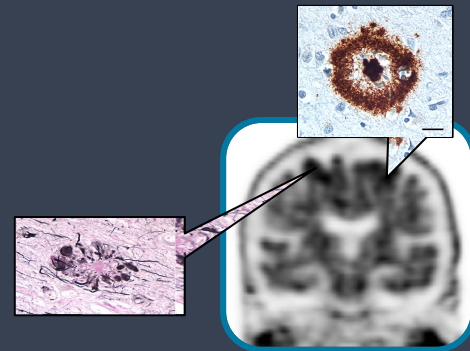
p

## Why quantification ?

- **Spot borderline** (most clinically relevant cases)
- Provide a more detailed picture (**regionality, relationship** with other biomarkers)

# What is amyloid PET?

- **In-vivo** assessment of  **$\beta$ -amyloid** in brain tissue
- **A $\beta$**  plaques: pathological hallmark of Alzheimer's disease
- In clinical practice the amy-PET is visually inspected (**binary classification**)



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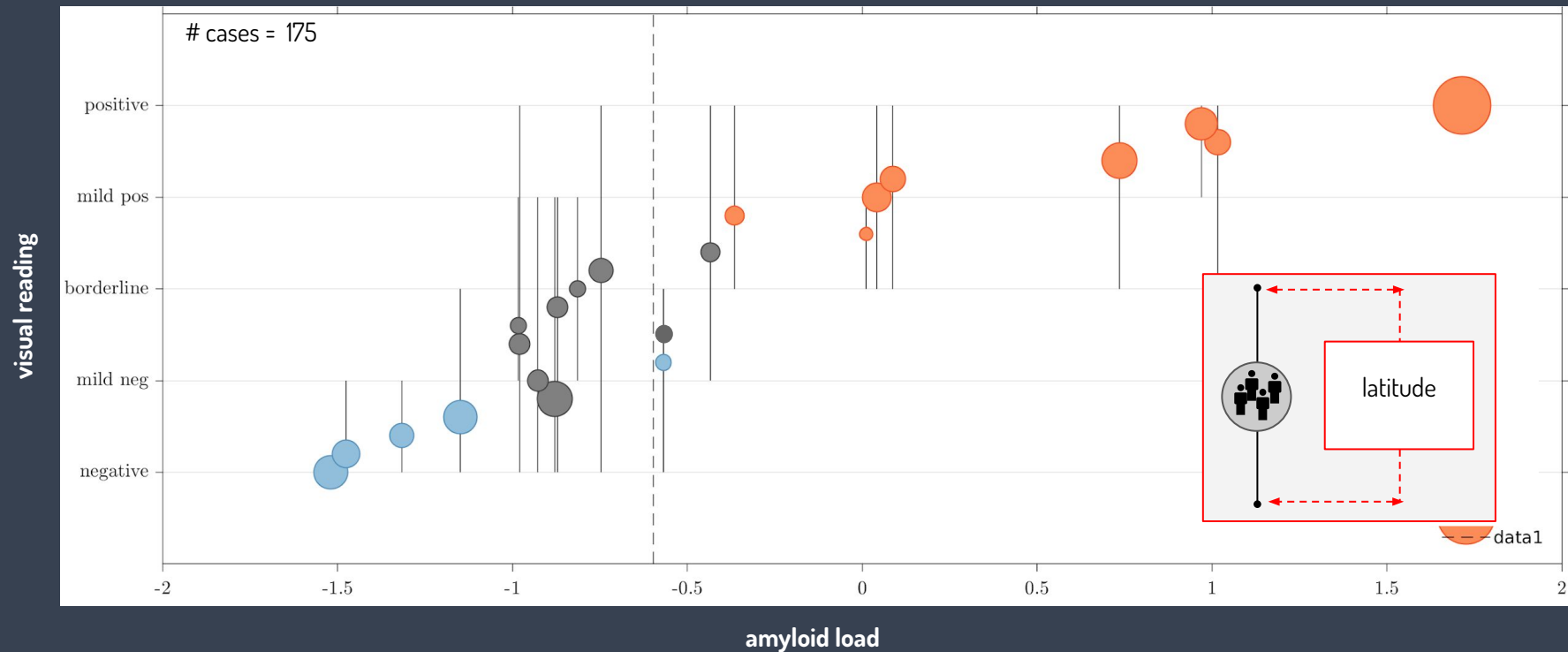
p

## Why quantification ?

- Spot borderline
- Provide a more detailed assessment with other biomarkers

Possibly even more critical with the approval of the first anti-amyloid treatment (June 2021)

# What happens in borderlines?

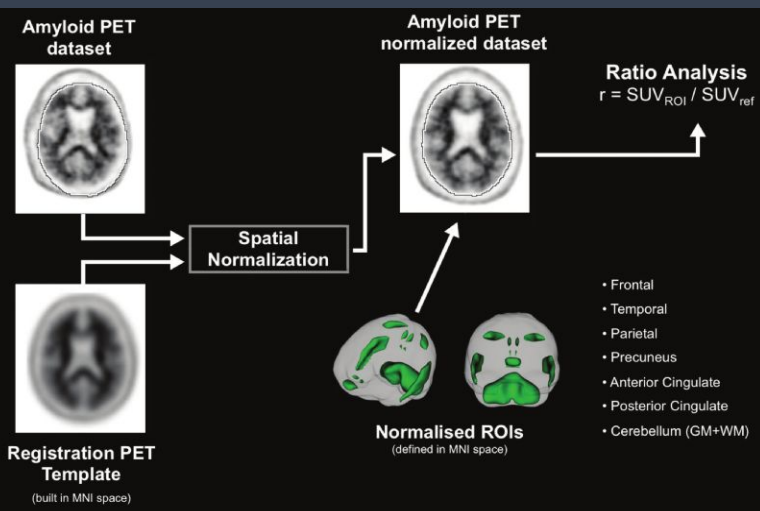


# Consolidated knowledge - SUVR



*Positron emission  
tomography-computed  
tomography standardized  
uptake values in clinical  
practice and assessing  
response to therapy*  
Semin Ultrasound CT MR  
Kinahan et al. (2010)

- register on a reference spatial frame (i.e. MNI)
- select reference (cerebellum, brain stem, ...) & target ROI (cortical)
- average counts (single/all ROI) and take the ratio



ratio of raw (mean) intensities  
**segmentation dependence**  
**fixed target ROI**  
**fixed reference ROI**

**very common** quantification approach

**automatic** analysis software **available**

SUVr values/outcome critically depend on ROI **definitions** and **positioning**

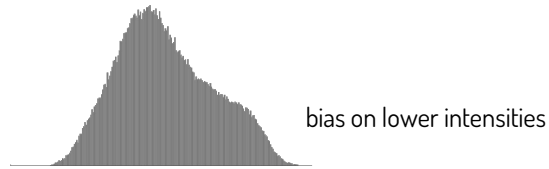
# Radiomic - ELBA



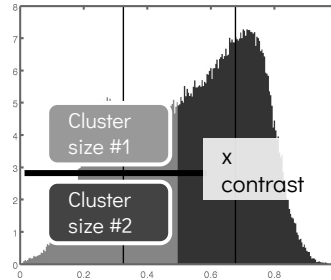
equal mix of geometric properties  
(sphericity) of iso-intensity surfaces &  
intensity statistics

**no need for ROIs, no need for reference uptake!**

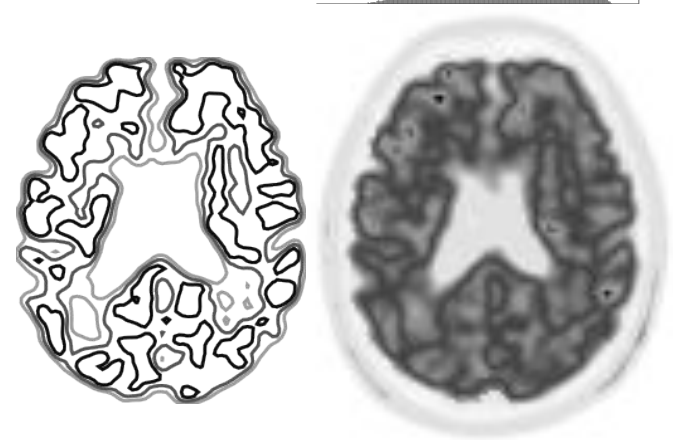
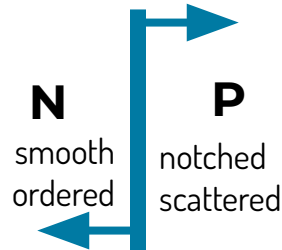
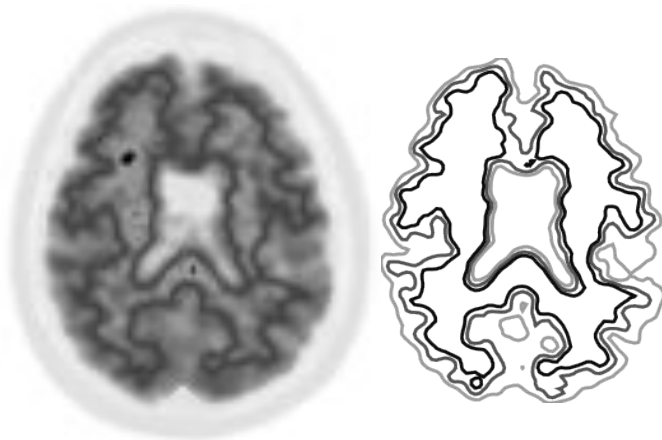
*SUVr-independent  
evaluation of brain  
amyloidosis*  
Journal of Alzheimer's  
Disease,  
Chincarini et al. (2016)



bias on lower intensities



bias on higher intensities

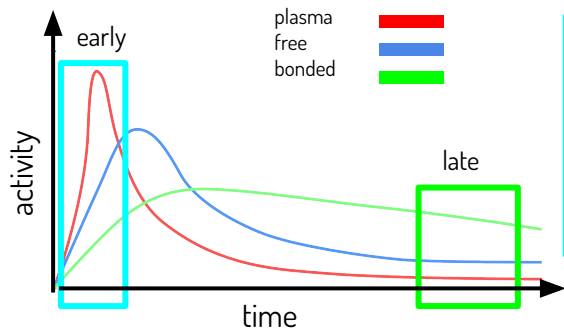


# Clinical model - TDr



*A kinetics-based  
approach to amyloid  
PET semi-quantification*  
EJNMMI,  
Chincarini et al. (2020)

**REQUIREMENT:** **early** acquisition, **proxy** of brain blood **perfusion** (Contractor 2012)

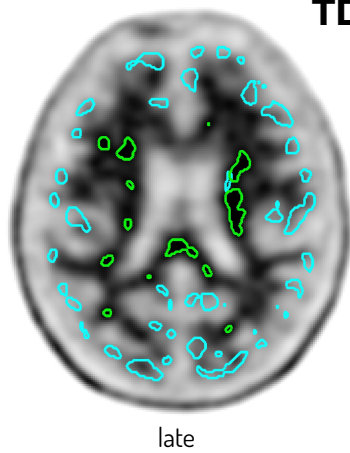
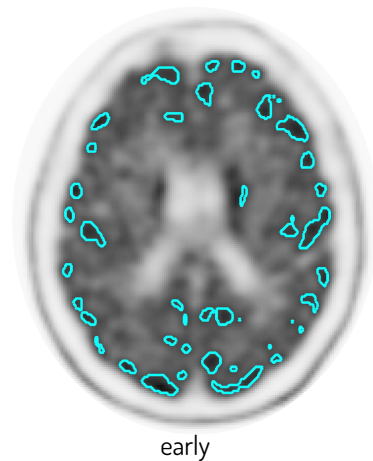


**Target**  
highest uptake in  
the **early** scan (CBF)  
(Osch 2009)

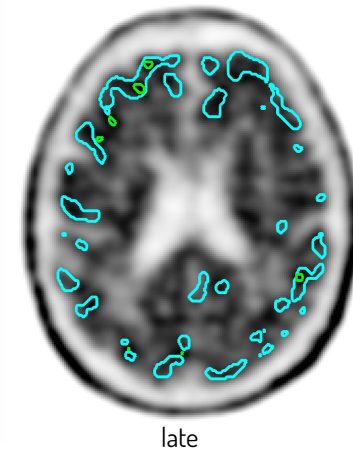
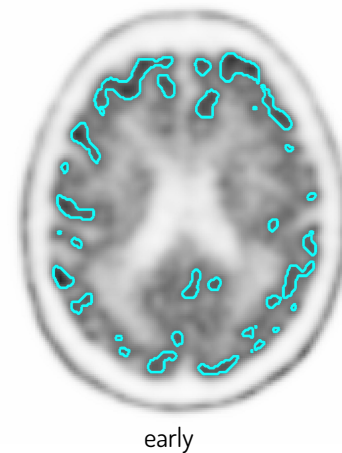
**Reference**  
highest uptake in the **late**  
scan (hot spot)  
(Fleisher 2017)

*no segmentation  
subject-dependent uptake ROI  
subject-dependent reference ROI*

$$\text{TDr} = \frac{\langle I_{\text{late}} \rangle_{\text{Target}}}{\langle I_{\text{late}} \rangle_{\text{Reference}}} = \frac{\text{[red box]}}{\text{[blue box]}}$$



< N | > P





# Validation



- 859 scan evaluated (615 clinical)
- Independent estimation of  $\beta$ -amyloid
- Tested on all commercially available tracer
- Excellent agreement with both visual and SUVR

	Accuracy	Specificity	Sensitivity
	[95% CI]		
TDr	0.945 [0.937 0.951]	0.933 [0.931 0.934]	0.957 [0.928 0.970]
SUVR	0.862 [0.853 0.874]	0.836 [0.831 0.848]	0.893 [0.864 0.906]
ELBA	0.955 [0.944 0.958]	0.958 [0.958 0.959]	0.953 [0.930 0.957]

European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:4097–4108  
https://doi.org/10.1007/s00259-022-05846-1

## ORIGINAL ARTICLE

### A comparison of advanced semi-quantitative amyloid PET analysis methods

Enrico Peira<sup>1,2</sup> · Davide Poggiali<sup>3</sup> · Matteo Pardini<sup>2,4</sup> · Annachiara Cagnin<sup>7</sup> · Andrea Chincarini<sup>1</sup> · Diego Cecchi<sup>1</sup>

Journal of Alzheimer's Disease 54 (2016) 1437–1457  
DOI 10.3233/JAD-160232  
IOS Press

### Standardized Uptake Value Ratio-Independent Evaluation of Brain Amyloidosis

Journal of Alzheimer's Disease 80 (2021) 383–396  
DOI 10.3233/JAD-201156  
IOS Press

### Probing the Role of a Regional Quotient in the Assessment of Amyloid PET

Enrico Peira<sup>a,b,\*</sup>, Matteo Grazzini<sup>b</sup>, Matteo Bauckneht<sup>c,d</sup>, Francesco Sensi<sup>b</sup>, Paola

Clinical and Translational Imaging (2021) 9:383–397  
https://doi.org/10.1007/s40336-021-00428-x

## PICTORIAL ESSAY

### Amyloid PET in the diagnostic workup of neurodegenerative diseases

Pierpaolo Alongi<sup>1</sup> · Agostino Chiaravallotti<sup>2,3</sup> · Valentina Bert<sup>4</sup> · Cecilia Vellani<sup>5</sup> · Giuseppe Trifiro<sup>6</sup> · Giulia Carli<sup>7</sup> · Andrea Chincarini<sup>8</sup> · Silvia Morbelli<sup>9,10</sup> · Daniela Perani<sup>7</sup> · Stelvio Sestini<sup>8</sup>

Received: 28 January 2021 / Accepted: 27 April 2021 / Published online: 23 June 2021  
© Italian Association of Nuclear Medicine and Molecular Imaging 2021

NeuroImage: Clinical 23 (2019) 101846

Contents lists available at ScienceDirect

NeuroImage: Clinical

Journal homepage: www.elsevier.com/locate/ynimg

### Semi-quantification and grading of amyloid PET: A project of the European Alzheimer's Disease Consortium (EADC)

A. Chincarini<sup>1,\*</sup>, E. Peira<sup>2,3</sup>, S. Morbelli<sup>4,5</sup>, M. Pardini<sup>6,7</sup>, M. Bauckneht<sup>8</sup>, J. Arbizu<sup>9</sup>, M. Castelo-Branco<sup>10</sup>, K.A. Rissina<sup>11</sup>, A. de Mendonça<sup>12</sup>, M. Didic<sup>13</sup>, M. Dottorini<sup>14</sup>, S. Engelborghs<sup>15</sup>, J. Garibotto<sup>16</sup>, E. Guedj<sup>17</sup>, L. Hausner<sup>18</sup>, J. Hugon<sup>19</sup>, J. Verhaeghe<sup>20</sup>, M. Riva<sup>21</sup>, M. Riva<sup>22</sup>, I. Santana<sup>23</sup>, U.P. Guerra<sup>24</sup>, F. Nobili<sup>25</sup>

Alzheimer 22, 1, 101846, Italy

Author's personal copy

European Journal of Nuclear Medicine and Molecular Imaging  
https://doi.org/10.1007/s00259-020-04689-y

## ORIGINAL ARTICLE

### A kinetics-based approach to amyloid PET semi-quantification

A. Chincarini<sup>1</sup> · E. Peira<sup>2,3</sup> · M. Corosu<sup>4</sup> · S. Morbelli<sup>5,6</sup> · M. Bauckneht<sup>7,8</sup> · S. Capitani<sup>9,10</sup> · M. Pardini<sup>11,12</sup> · D. Arnaldi<sup>13,14</sup> · C. Vellani<sup>15</sup> · D. D'Ambrosio<sup>16</sup> · V. Garibotto<sup>17,18</sup> · F. Assal<sup>19,20</sup> · B. Paghera<sup>21</sup> · G. Savelli<sup>22</sup> · A. Stefanelli<sup>23</sup> · U. Guerra<sup>24</sup> · F. Nobili<sup>25</sup>

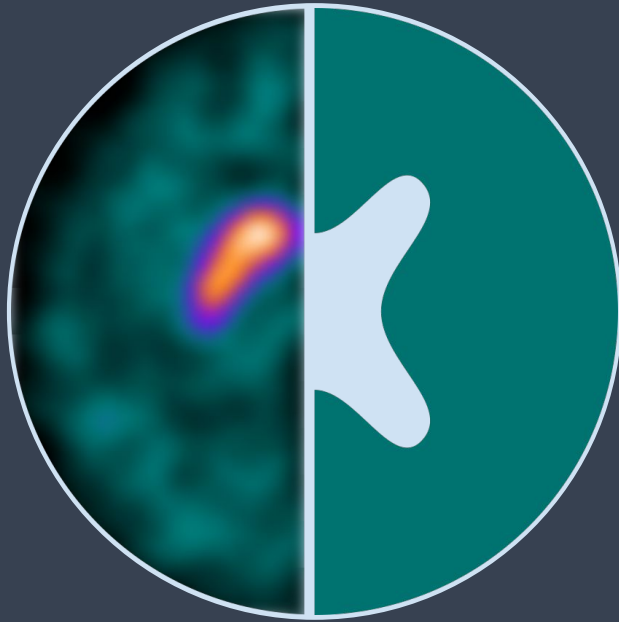
Bauckneht et al. Alzheimer's Research & Therapy (2018) 10:35  
https://doi.org/10.1186/s13195-018-0060-y

## RESEARCH

## Open Access

### Metabolic correlates of reserve and resilience in MCI due to Alzheimer's Disease (AD)

Matteo Bauckneht<sup>1,2</sup>, Andrea Chincarini<sup>3</sup>, Roberta Piva<sup>4,5</sup>, Dario Arnaldi<sup>6,7</sup>, Nicola Girtler<sup>8,9</sup>, Federico Massa<sup>10</sup>, Matteo Pardini<sup>11</sup>, Matteo Grazzini<sup>12</sup>, Hulya Eftekar<sup>13</sup>, Marco Pagan<sup>14</sup>, Gianmario Sambucetti<sup>15</sup>, Flavio Nobili<sup>16</sup> and Silvia Morbelli<sup>17</sup>

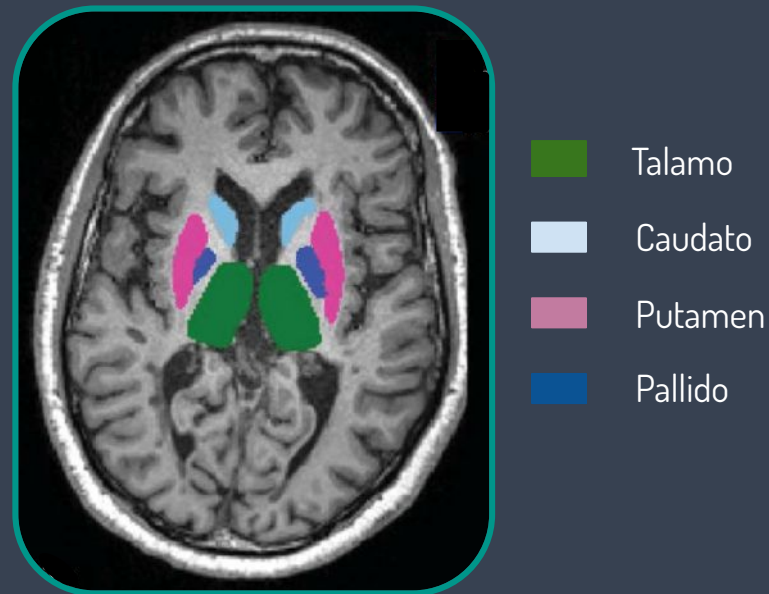
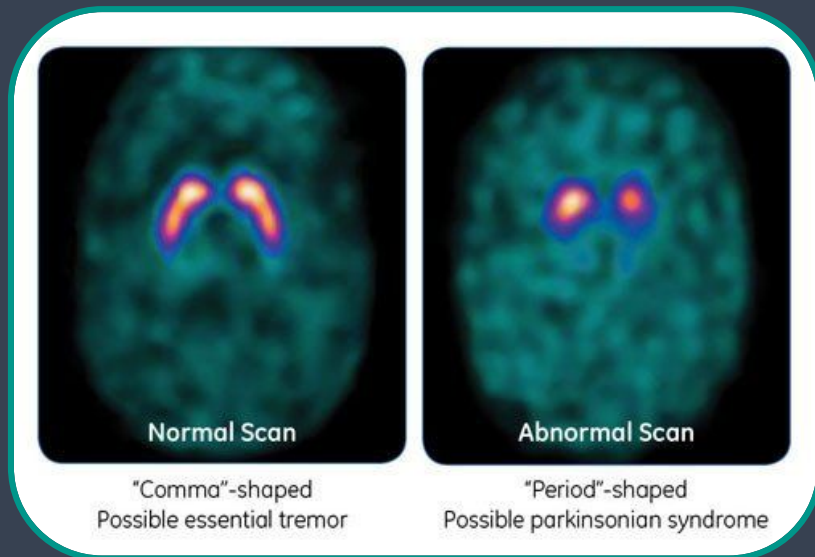


DOPAMINE  
TRANSPORTER



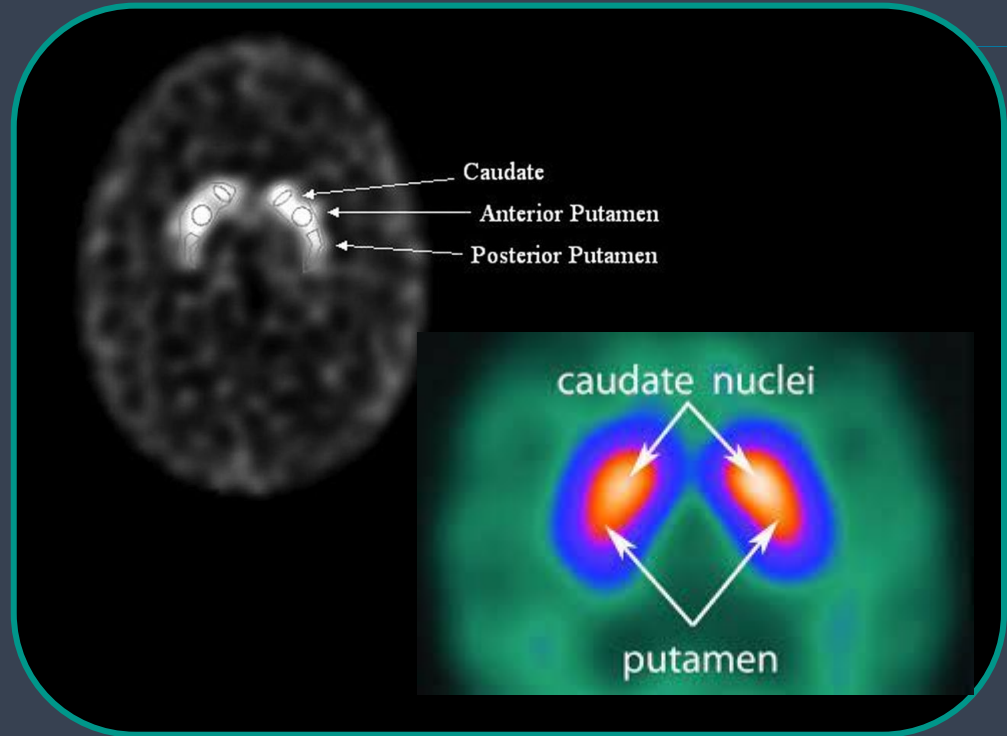
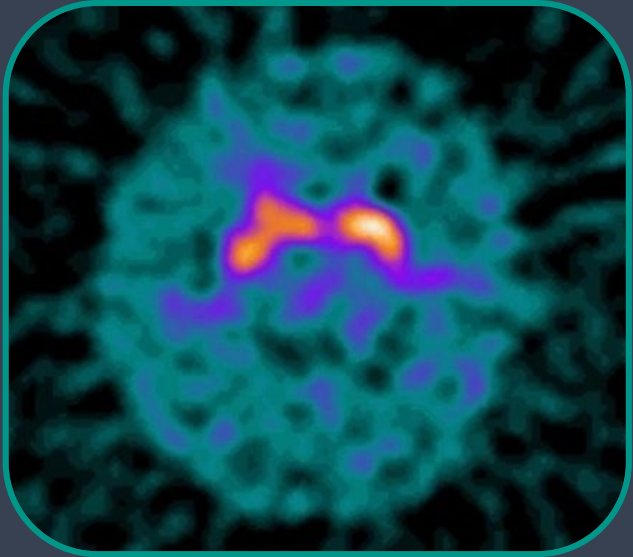
# What is DaT-SPECT?

- $^{123}\text{I}$ -loflupane with SPECT: allow **in-vivo** assessment of **DaT** (dopamine transporter)
- **Marker** of nigrostriatal **dopaminergic** network **integrity** that is impaired in **Parkinson**
- **Visual assessment** in **clinical** practice (putamen uptake reduction, right-left imbalance)



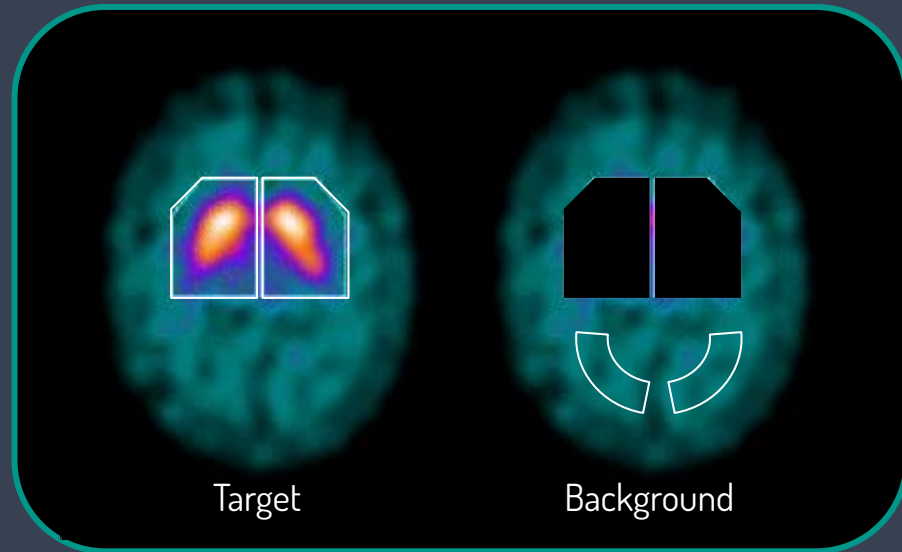
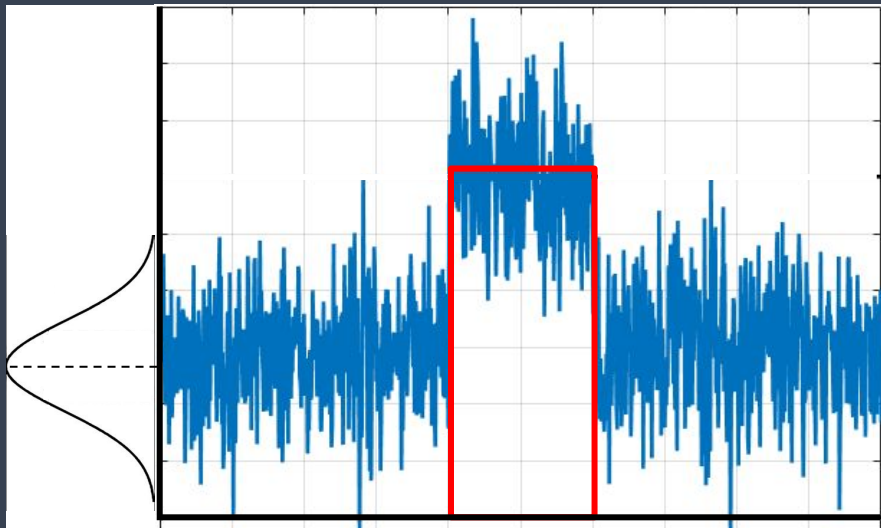
# Main issues

- **PVE:** Low SPECT resolution and small target regions (6-12mm)
- Low **S/N ratio**



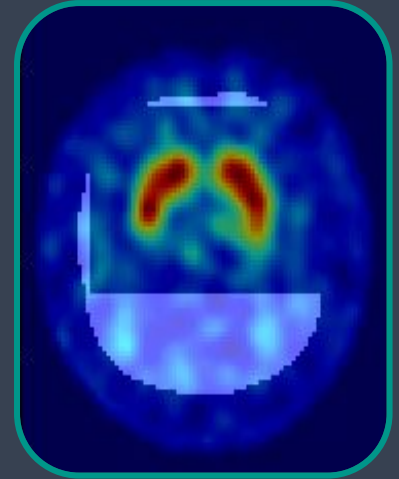
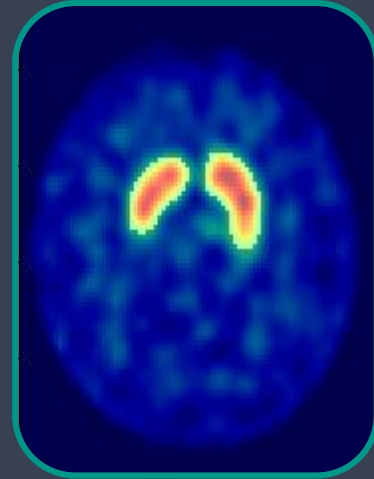
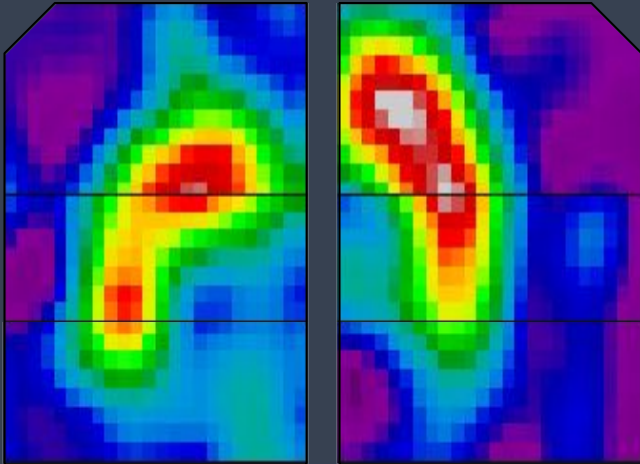
**alignment** and spatial **normalisation** are tricky!

- MNI normalization
- Assumption: no signal outside striatum
- Target voxels are distance weighted from the background distribution
- SBR (striatal vs occipital)

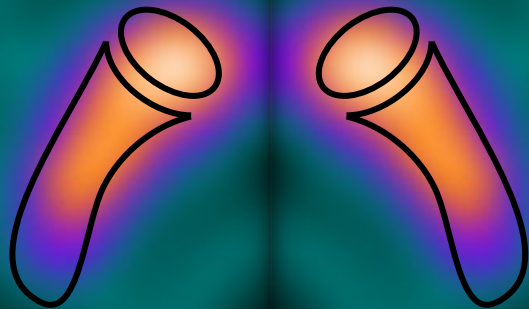


$$SBR = \frac{C_{Tgt} - C_{Bckg}}{C_{Bckg}}$$

- MNI normalization
- Coarse segmentation based on the distance of striatal voxels from the background
- Left and right volume (PDVol)
- Average intensity / Background (PDIdx)

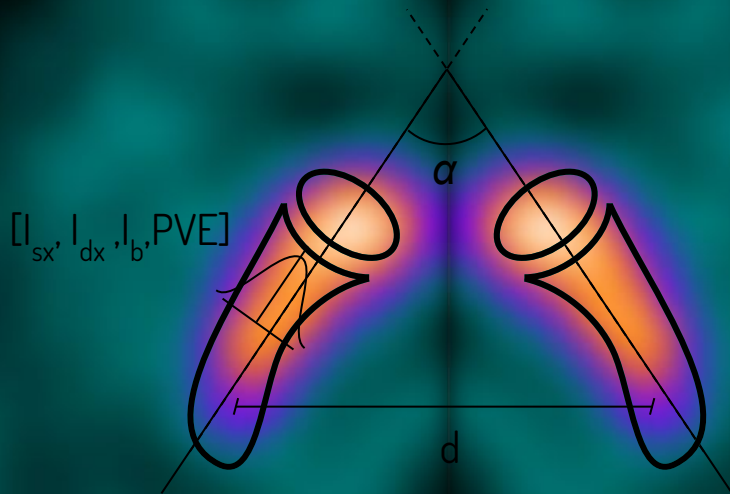


# Clinical model - Striatal Matched SBR



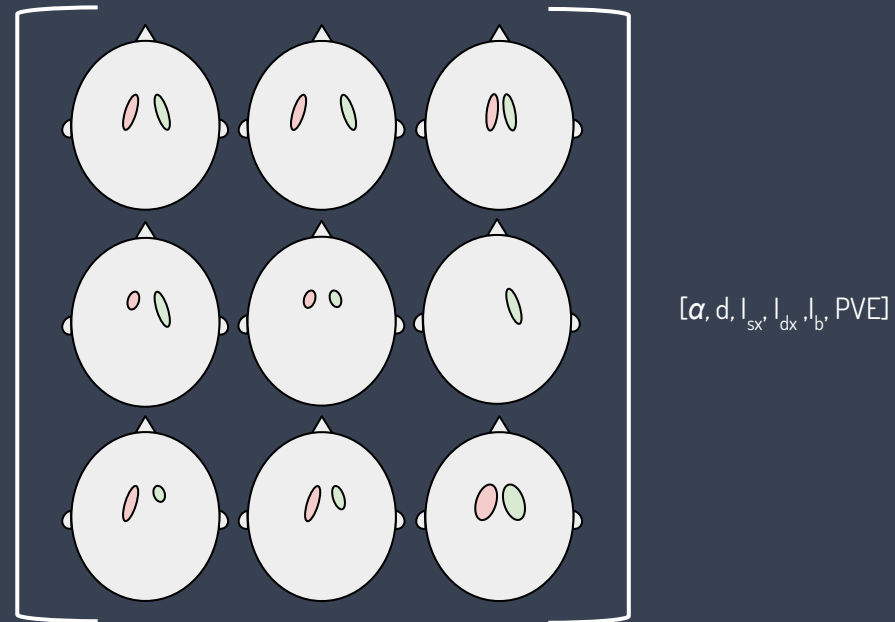
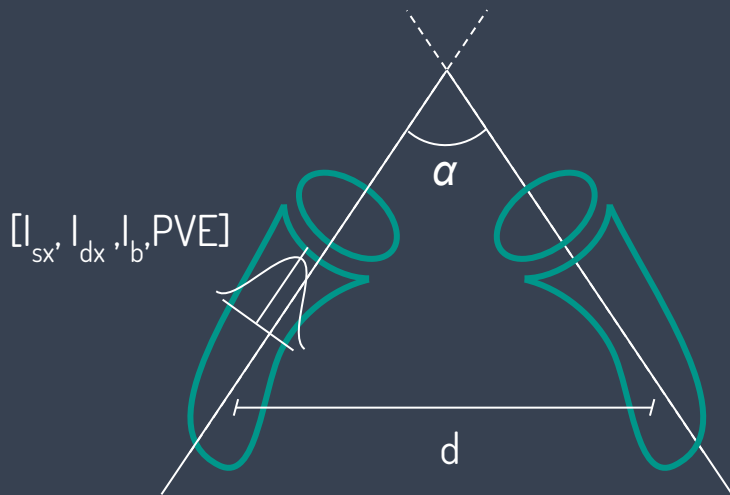
Dealing with data variability that affect processing

# Clinical model - Striatal Matched SBR



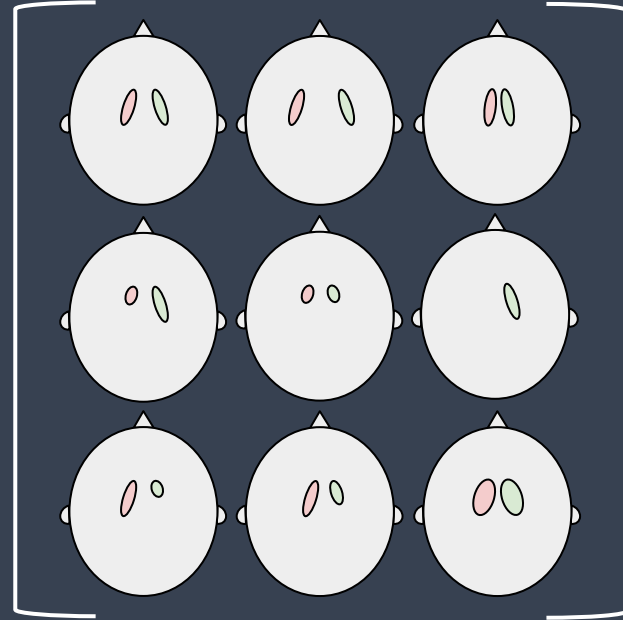
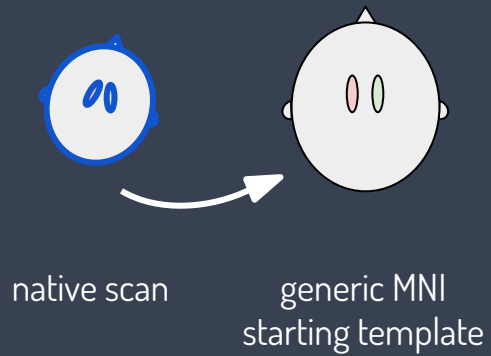
Modelling pathophysiological characteristic (left/right/background intensity, tilting, distance, ...)

# Clinical model - Striatal Matched SBR



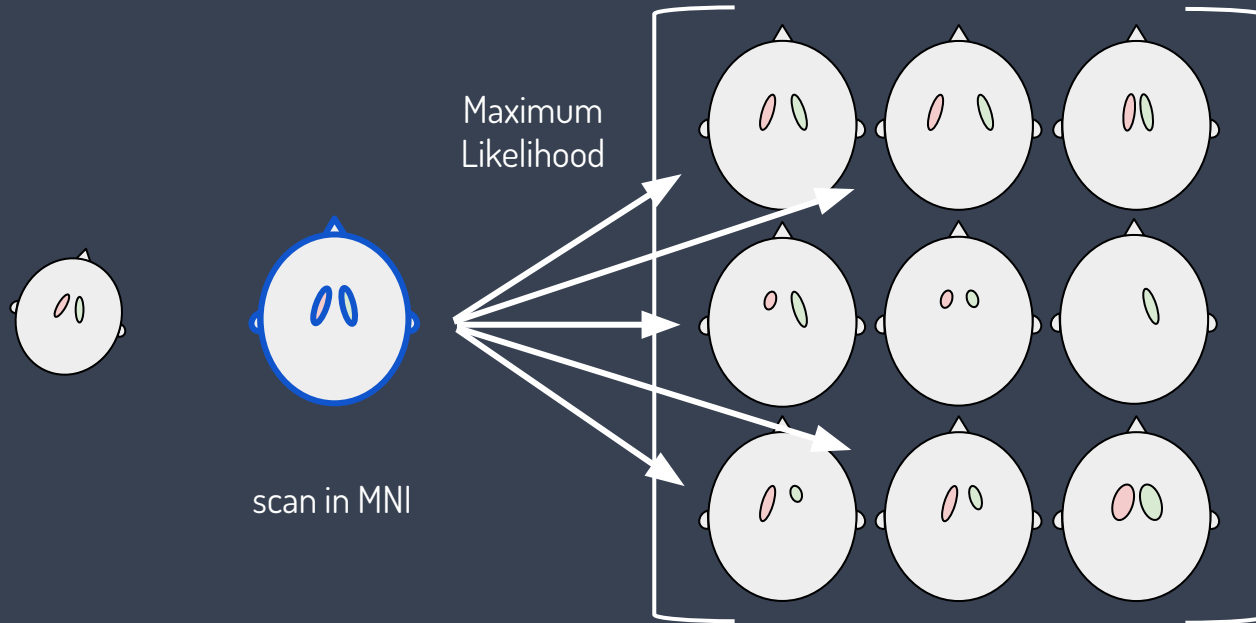
MNI template space

# Clinical model - Striatal Matched SBR

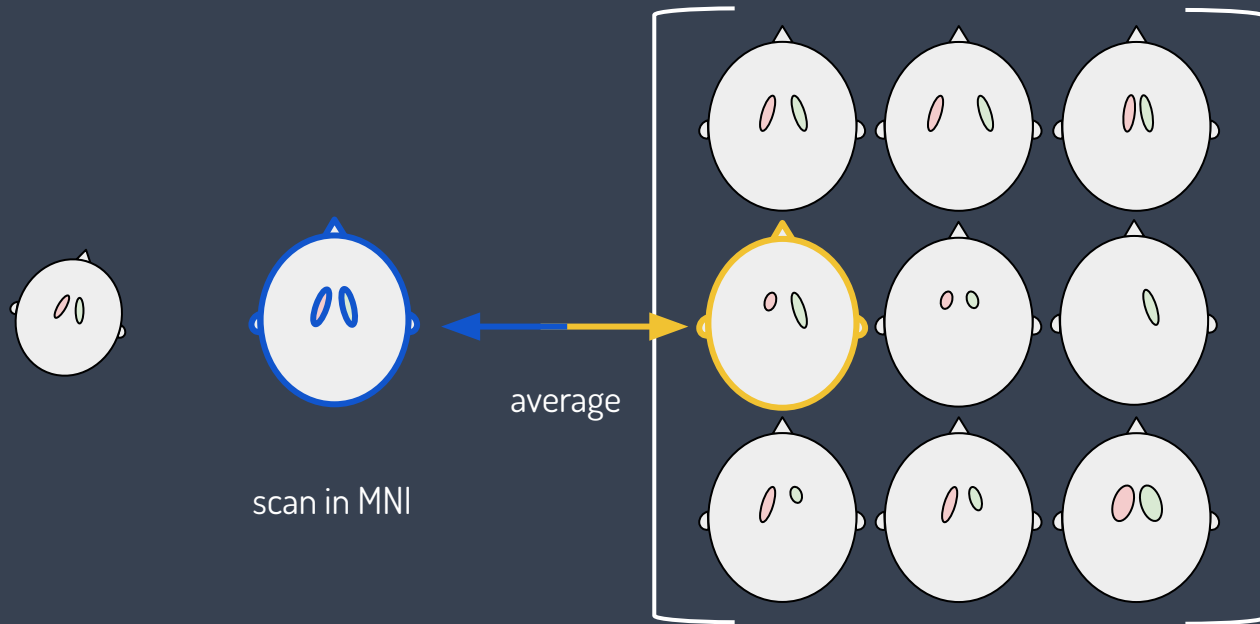




# Clinical model - Striatal Matched SBR



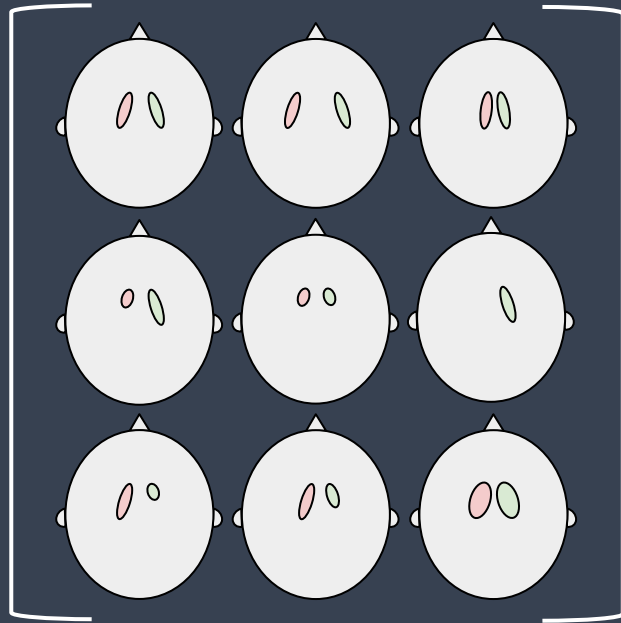
# Clinical model - Striatal Matched SBR



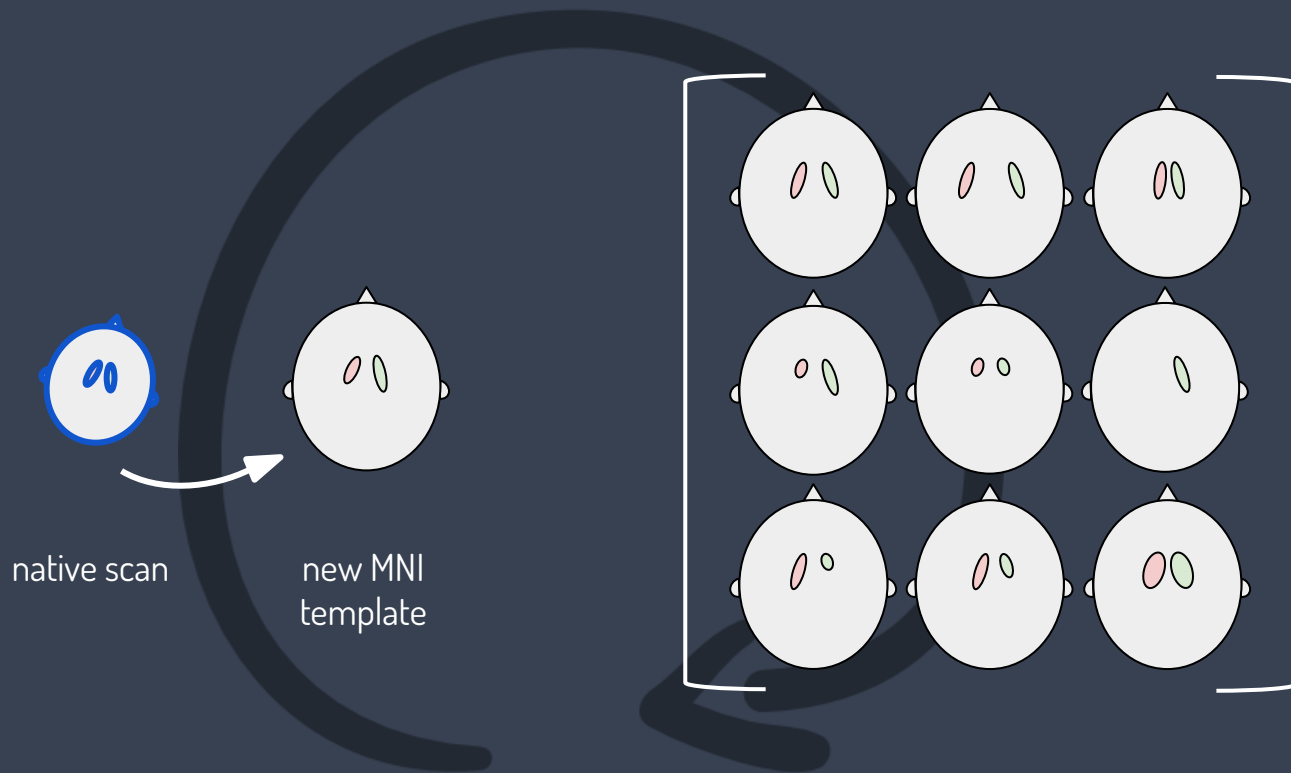
# Clinical model - Striatal Matched SBR



new MNI  
template



# Clinical model - Striatal Matched SBR



Iterative registration on a progressively averaging template

# Clinical model - Striatal Matched SBR



Multiple registration on a progressively averaged model allows the model (i.e. the estimated parameters) to converge to the mean parameters that best represent the input image, while at the same time overview the parameter precision



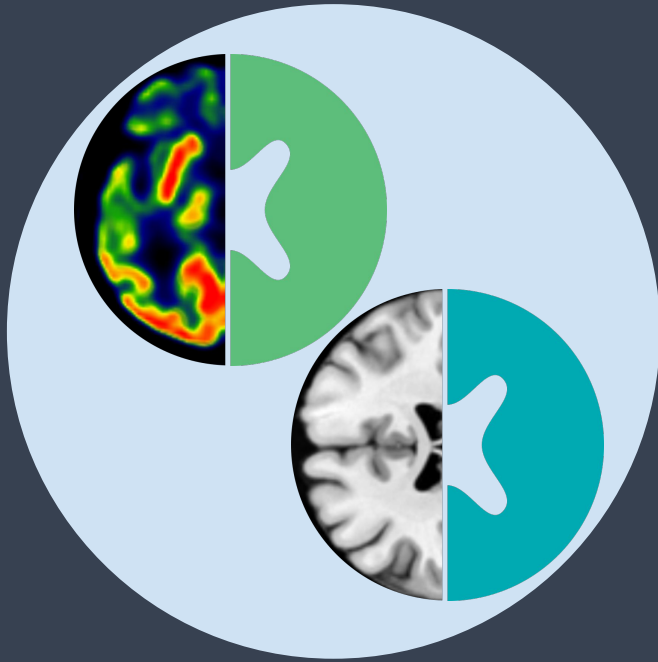
By adding parameters I can update the method with the pathophysiological model



You pay with computational cost (approx 1 min x registration on a “decent” hardware (multicore, min 32 GB memory) and possible convergence problems, but you can tune the iterations to achieve desired statistical error

$$SBR = \frac{C_{Tgt} - C_{Bckg}}{C_{Bckg}}$$

Iterative registration on a progressively averaging template



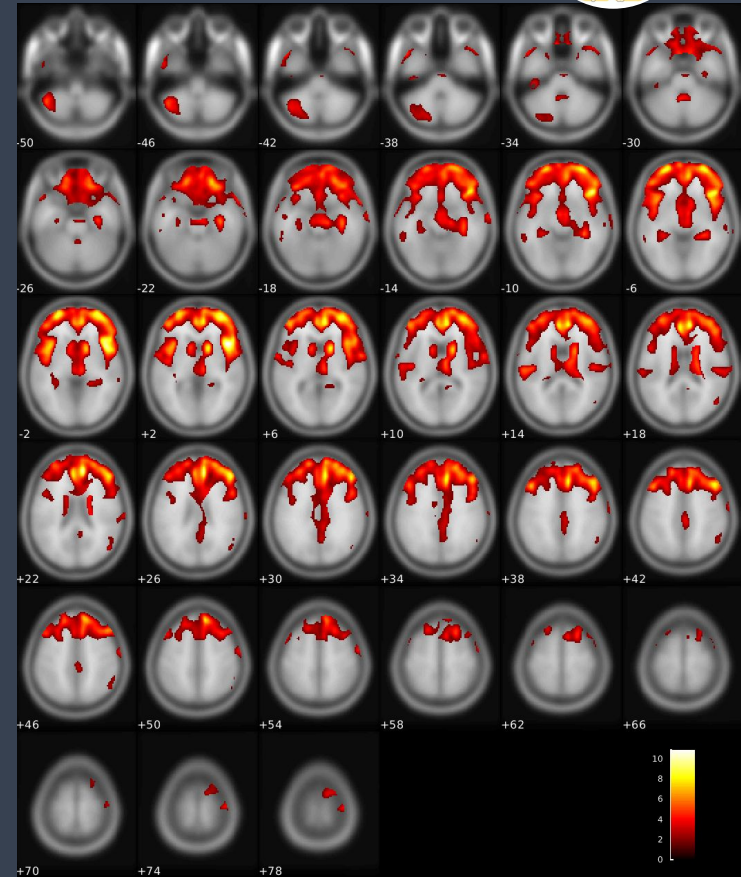
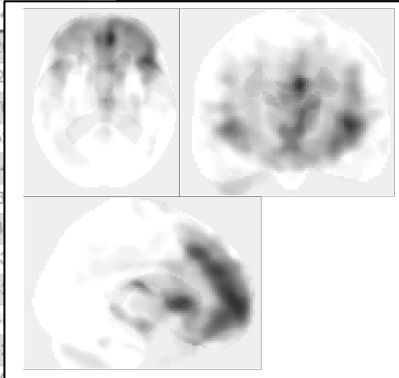
# GLUCOSE HYPOMETABOLISM & NEURODEGENERATION



# Consolidated knowledge - Voxel-wise (SPM)

- Voxel-wise analysis in SPM
- FDG hypometabolism T-maps

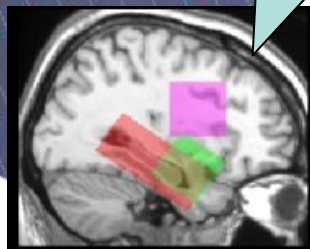
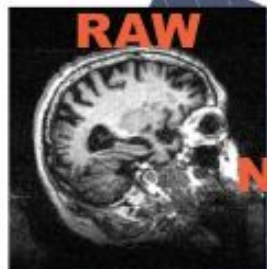
set-level		cluster-level			peak-level					coords	
$p$	$c$	$p_{FWE-corr}$	$q_{FDR-corr}$	$k_E$	$p_{uncorr}$	$p_{FWE-corr}$	$q_{FDR-corr}$	$T$	$(Z_E)$	$p_{uncorr}$	[mm]
1.000	9	0.000	0.000	53557	0.000	0.000	0.000	10.80	Inf	0.000	(44, 16, 0)
						0.000	0.000	10.18	Inf	0.000	(10, 44, 22)
						0.000	0.000	9.76	Inf	0.000	(46, 26, -10)
		0.962	0.863	1130	0.044	0.009	0.001	5.32	5.04	0.000	(-4, 10, 10)
						1.000	0.236	3.17	3.10	0.001	(-2, 10, 10)
		1.000	0.972	217	0.354	0.443	0.024	4.15	4.01	0.000	(-2, 10, 10)
		1.000	0.972	218	0.353	0.751	0.048	3.87	3.75	0.000	(7, 10, 10)
						1.000	0.886	2.14	2.12	0.017	(6, 10, 10)
						1.000	0.954	1.97	1.96	0.025	(6, 10, 10)
		1.000	0.972	548	0.146	0.927	0.084	3.65	3.54	0.000	(-3, 10, 10)
						1.000	0.575	2.63	2.59	0.005	(-3, 10, 10)
						1.000	0.969	1.91	1.90	0.029	(-3, 10, 10)
		1.000	0.972	108	0.521	0.998	0.173	3.32	3.24	0.001	(-4, 10, 10)
		1.000	0.972	146	0.451	0.999	0.193	3.27	3.19	0.001	(4, 10, 10)
						1.000	0.893	2.11	2.09	0.018	(5, 10, 10)
		1.000	0.972	147	0.449	1.000	0.575	2.64	2.60	0.005	(5, 10, 10)
						1.000	0.876	2.17	2.15	0.016	(54, -48, 46)
		1.000	0.972	161	0.427	1.000	0.703	2.48	2.45	0.007	(-56, -42, -12)
						1.000	0.987	1.83	1.82	0.035	(-56, -30, -22)



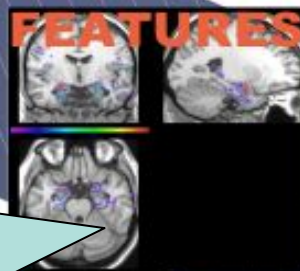
SPM report table.

Solid grey line separates significant clusters each level.  $q_{peakFWE-corr} < 0.05$ .

# Radiomic - Global Disease Index



**VOI placement**  
7 MTL volumes



## Classification

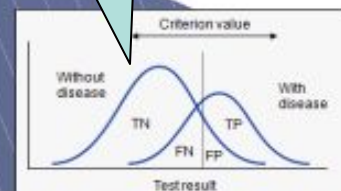
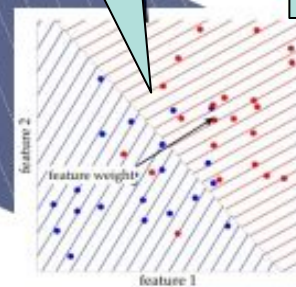
SVM classifier take feature subset from the RF and output the distance between the input set and the discriminating hyper surface.

## Biomarker

A number is assigned to each input scan ranging from 1 (normalcy) to -1 (AD neurodegeneration)

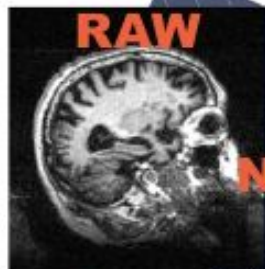
## Relevant regions & features

A RF algorithm select those who discriminates CTRL / AD





# Radiomic - Global Disease Index



**VOI placement**  
7 MTL volumes

## Classification

SVM classifier take feature subset from the RF and output the distance between the input set and the discriminating hyper surface.

## Biomarker

## Relevant regions & feat

A RF algorithm select those who discr  
AD

NeuroImage 58 (2011) 469–480

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NeuroImage

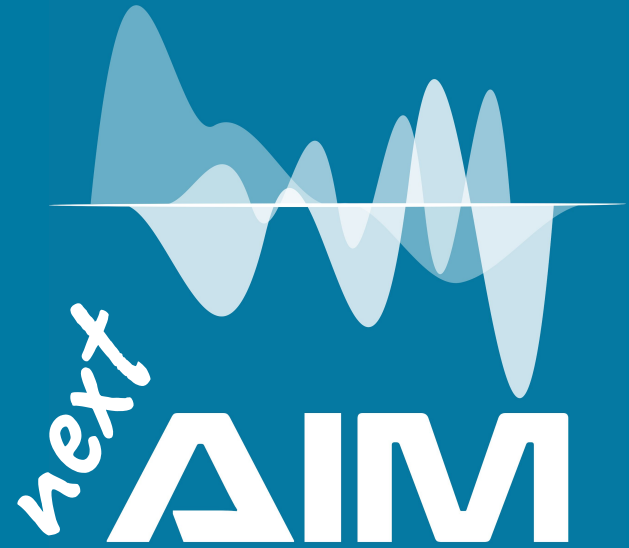
journal homepage: [www.elsevier.com/locate/ynimg](http://www.elsevier.com/locate/ynimg)



## Local MRI analysis approach in the diagnosis of early and prodromal Alzheimer's disease ☆

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and The Alzheimer's Disease Neuroimaging Initiative

# Artificial Intelligence in Medicine



# Thank you !

Enrico Peira  
next\_AIM annual meeting  
14.02.2023, Milano



DORIAN  
evolving neuroimaging

