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CRC In vivo Imaging

Investigating demyelination, iron accumulation, and synaptic loss in Alzheimer's disease using multimodal imaging techniques

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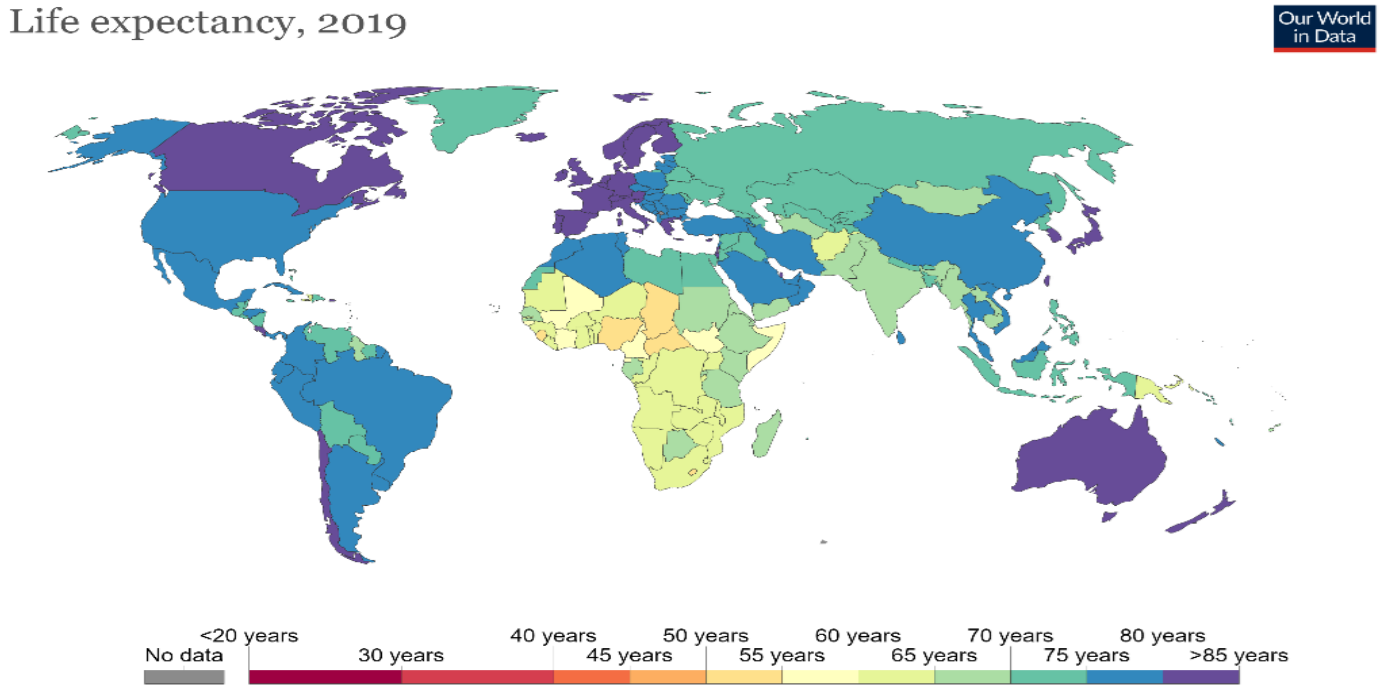
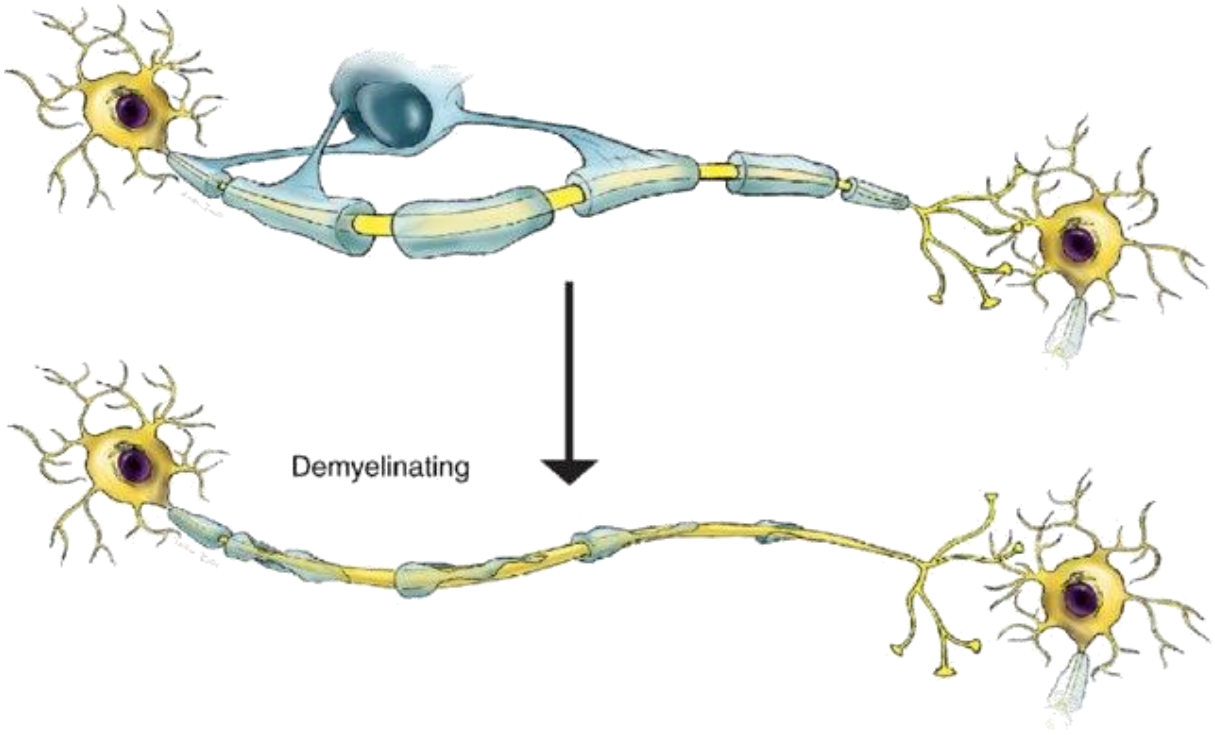


The total number of people with AD dementia in 2050 is projected to be 13.8 million, with 7.0 million aged 85 years or older in the US.

By 2050, the number of people aged 65 and older with Alzheimer's dementia is projected to reach 12.7 million. (ONLY IN the US)

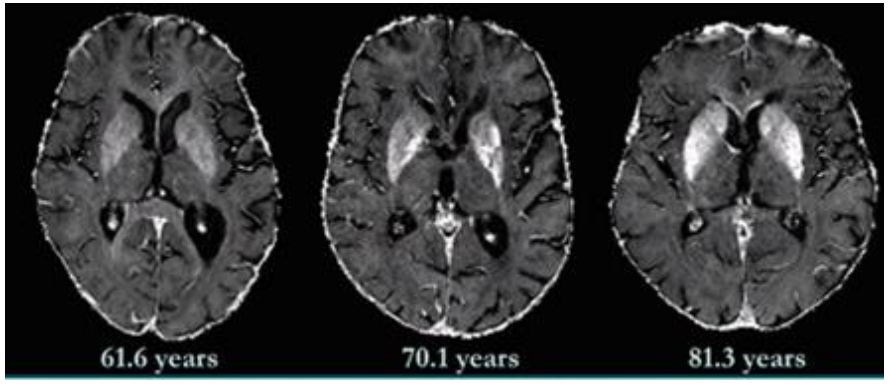
57 million people were living with dementia globally in 2019, a number expected to rise to 153 million by 2050.

- Hebert, L. E, et. Al., 2013 *Neurology*. https://doi.org/10.1212/WNL.0b013e31828726f5
- 2022 Alzheimer's Disease Facts and Figures, Special Report More Than Normal Aging: Understanding Mild Cognitive Impairment
- Alzheimer's disease international, 2022


Demyelinating


ZZZ


Family
History


61.6 years
70.1 years
81.3 years

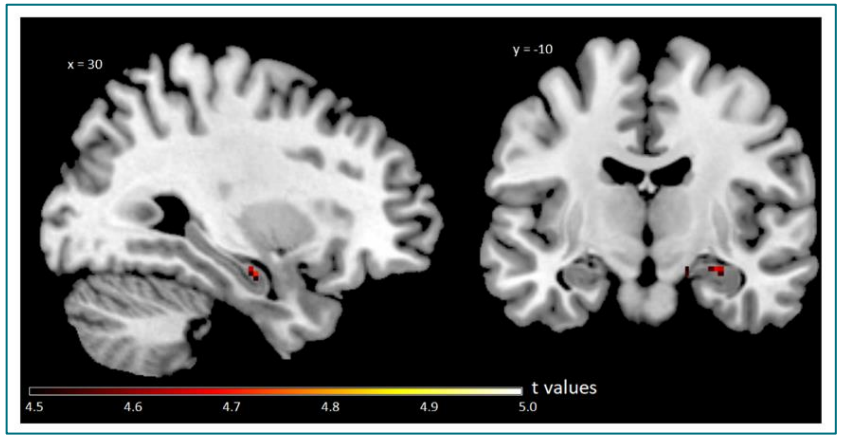
European Journal of Nuclear Medicine and Molecular Imaging (2020) 47:390–402
https://doi.org/10.1007/s00259-019-04461-x

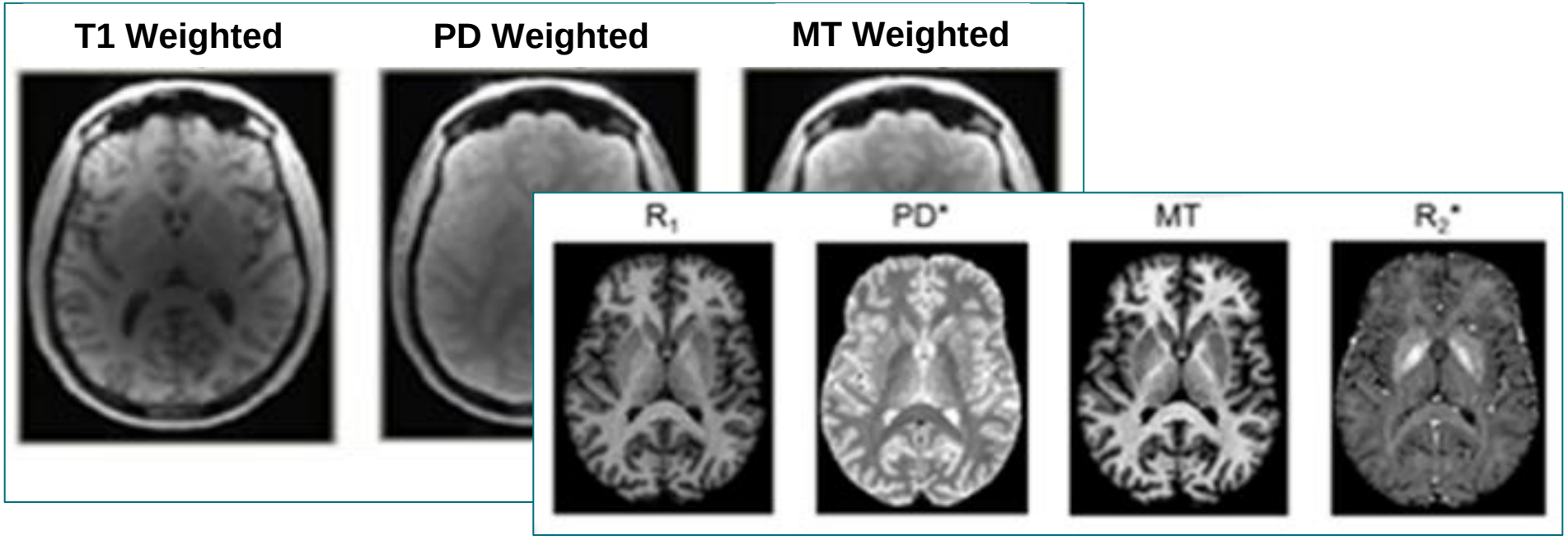
ORIGINAL ARTICLE

Check for updates

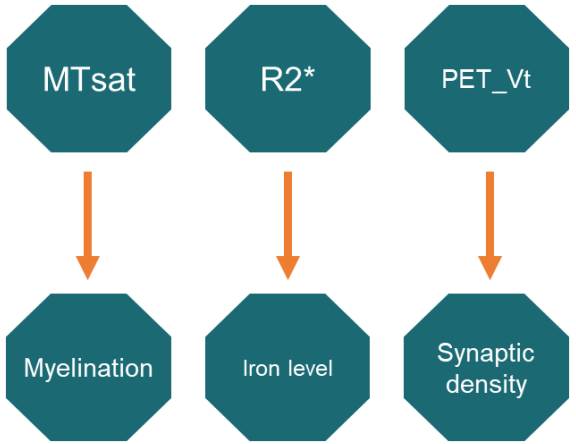
In vivo imaging of synaptic loss in Alzheimer's disease with [18F] UCB-H positron emission tomography

Christine Bastin[1] · Mohamed Ali Bahri[1] · François Meyer[1] · Marine Manard[1] · Emma Delhaye[1] · Alain Plenevaux[1] · Guillaume Becker[1] · Alain Seret[1] · Christine Mella[1] · Fabrice Giacomelli[1] · Christian Degueldre[1] · Evelyne Balteau[1] · André Luxen[1] · Eric Salmon[1]

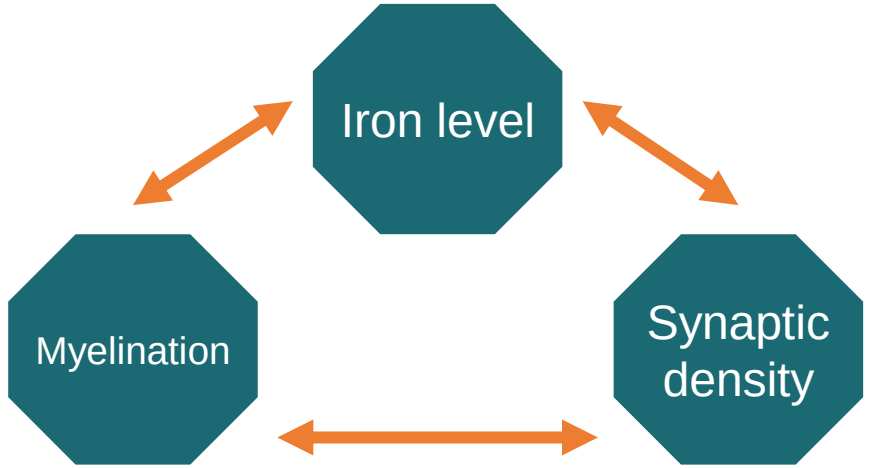




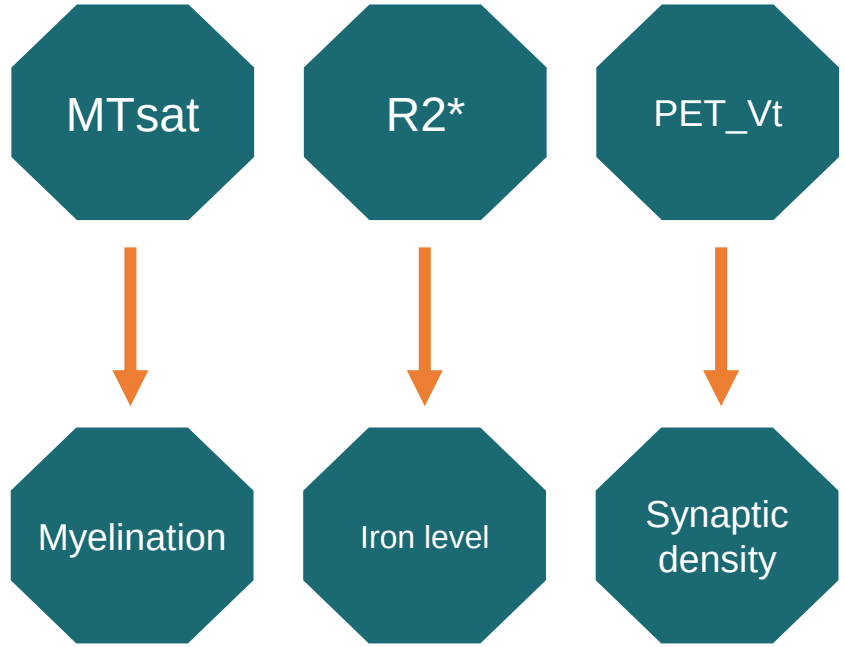
Characterize patients from healthy controls using different image-derived biomarkers for AD



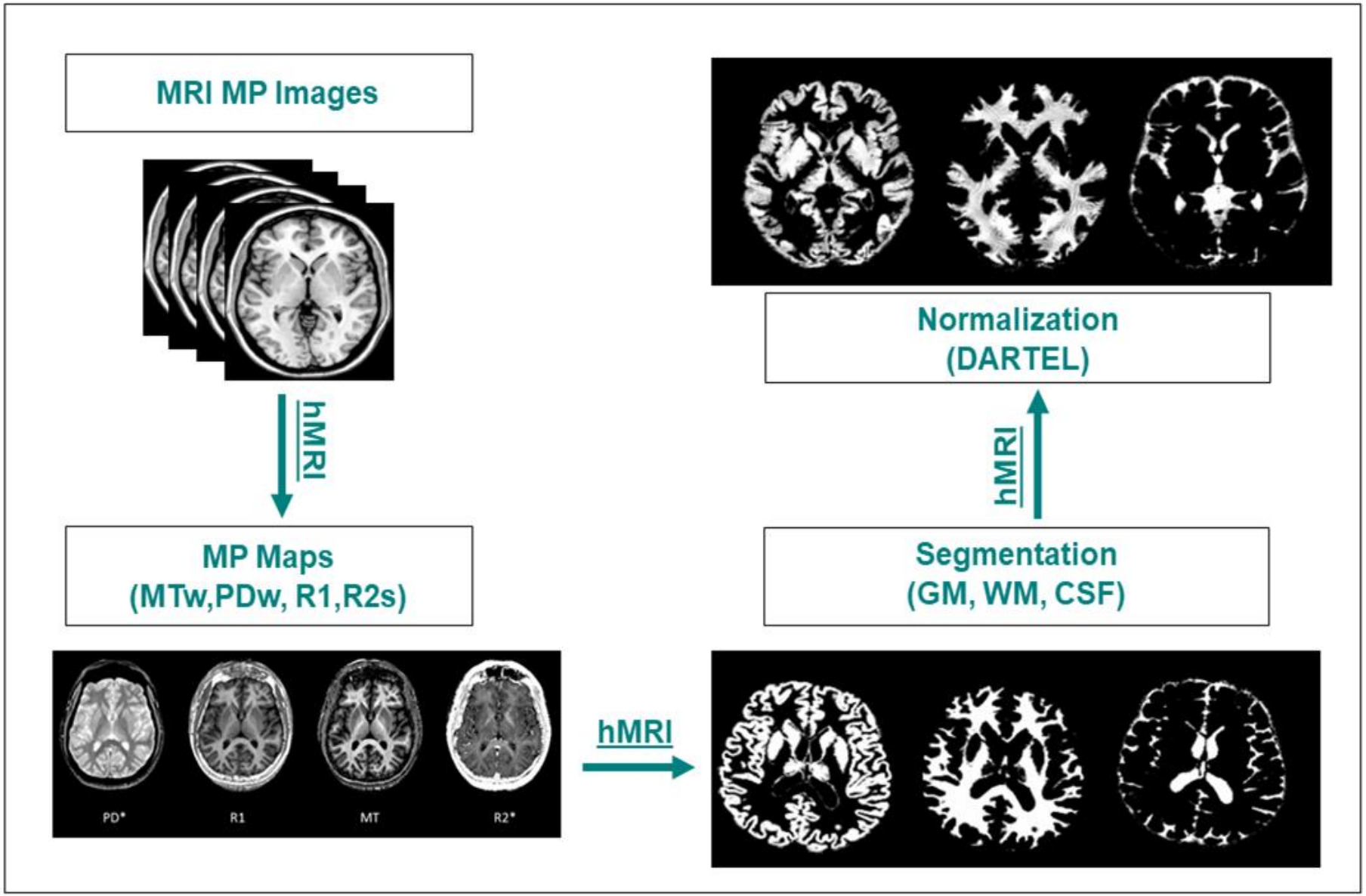
Investigate the association of image-derived markers in a multivariate model



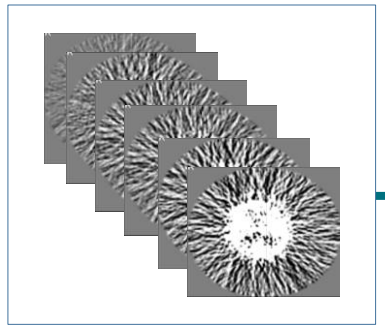
Data sets	# Subjects	Gender	Age Range
Alzheimer's disease	**24** (11 males - 13 females)		60-80
Healthy control	**19** (9 males -10 females)		



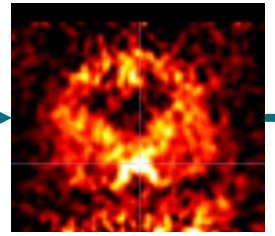
Quantitative maps creation



Vt maps creation



First PET frames



Carotid Seed/carotid

For the mid-time of each PET frame

The IDIF is estimated for the carotid region

IDIF estimation

PMOD

Kinetic modeling

PMOD

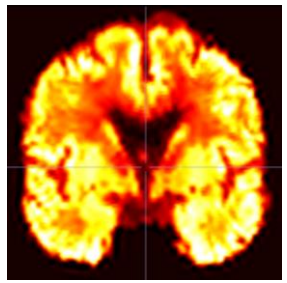
Logan analysis

PETPVC

Corrected for PVE

PMOD

Vt maps



Z-transformation

All maps are in the MNI space… → Good enough for the univariate analysis

Each modality represents a different property and unit! → The data is not comparable, and we cannot use them in a multivariate analysis

Z-transformation

$$\boldsymbol{Y = X\beta + \varepsilon}$$

MSPM

Univariate GLM:

$$X = \begin{bmatrix} AD_m & 0 & age & sex \\ 0 & HC_m & age & sex \end{bmatrix}_{43\times4} \quad \beta = \begin{bmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{bmatrix}$$

Test the difference between groups using one modality

$$H_0: C\beta = 0$$
$$H_1: C\beta \neq 0$$

Between Subject contrast $\quad C = [1 \quad -1 \quad 0 \quad 0]$

Multivariate GLM:

$$X = \begin{bmatrix} AD_{MT} & 0 & age & sex \\ AD_{R2s} & 0 & age & sex \\ AD_{PET} & 0 & age & sex \\ 0 & HC_{MT} & age & sex \\ 0 & HC_{R2s} & age & sex \\ 0 & HC_{PET} & age & sex \end{bmatrix}_{129\times4} \quad B = \begin{bmatrix} \mu_{111} & \mu_{112} \\ \mu_{121} & \mu_{122} \\ \mu_{211} & \mu_{212} \\ \mu_{221} & \mu_{222} \end{bmatrix}$$

Test the difference between groups using all modalities at once

$$H_0: CBL = 0$$
$$H_1: CBL \neq 0$$

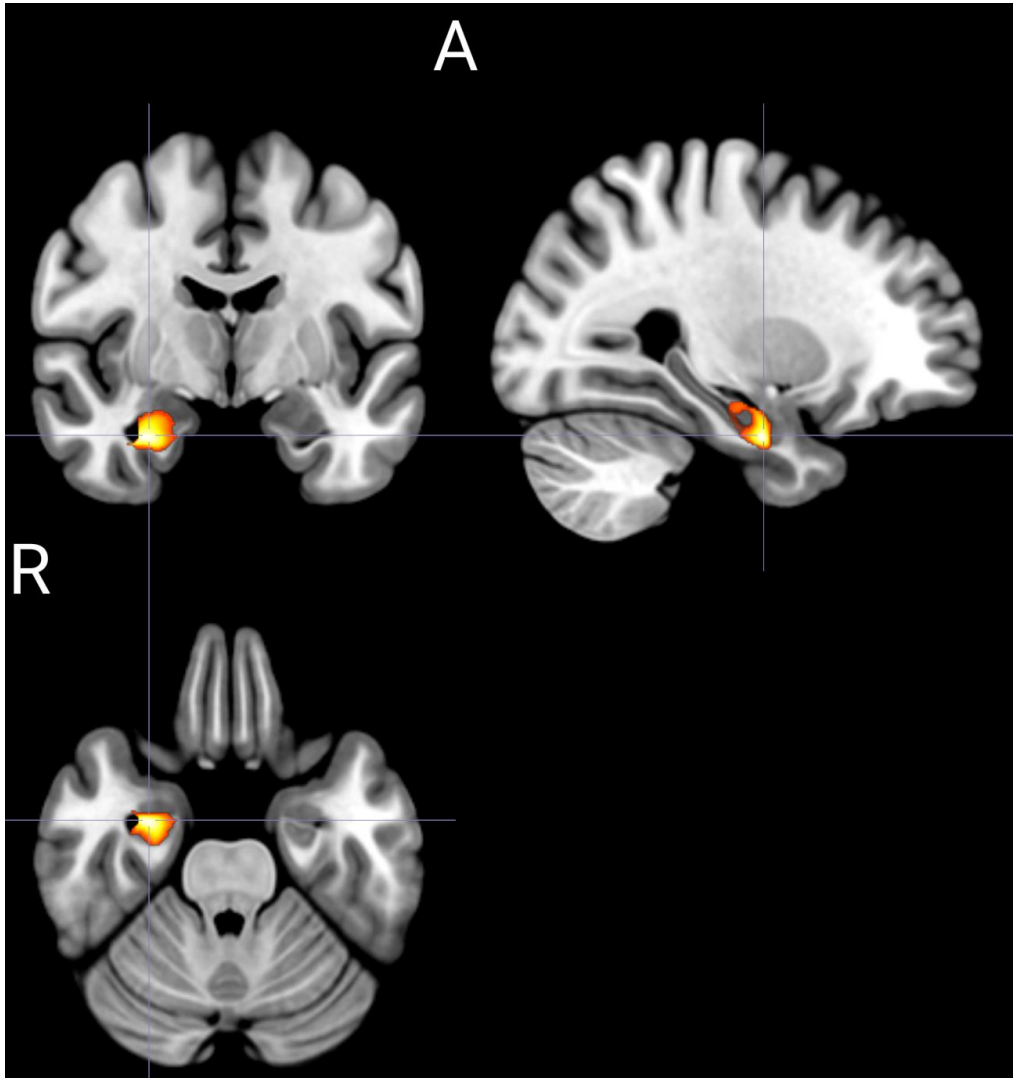
Within Subject parameter $\quad L = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}_{3\times3}$

Between Subject contrast $\quad C = [1 \quad -1 \quad 0 \quad 0]$

* Here “m” represents different modalities

L. Gyger *et al.*, *NeuroImage,* May 2021, doi: 10.1016/j.neuroimage.2021.117895.

Univariate GLM — MTsat



Statistics: *p-values adjusted for search volume*

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	F	(Z_E)	p_{uncorr}			
0.845	3	0.001	0.001	1993	0.000	0.201	0.186	28.25	4.43	0.000	31	-7	-27
						0.520	0.307	23.72	4.12	0.000	37	-21	-12
						0.782	0.307	21.04	3.91	0.000	20	-11	-20
		0.972	0.940	131	0.203	0.604	0.307	22.86	4.06	0.000	-66	-49	-15
		0.636	0.486	315	0.057	0.997	0.752	16.28	3.48	0.000	-24	-10	-25
						0.999	0.816	15.48	3.40	0.000	-19	-6	-35

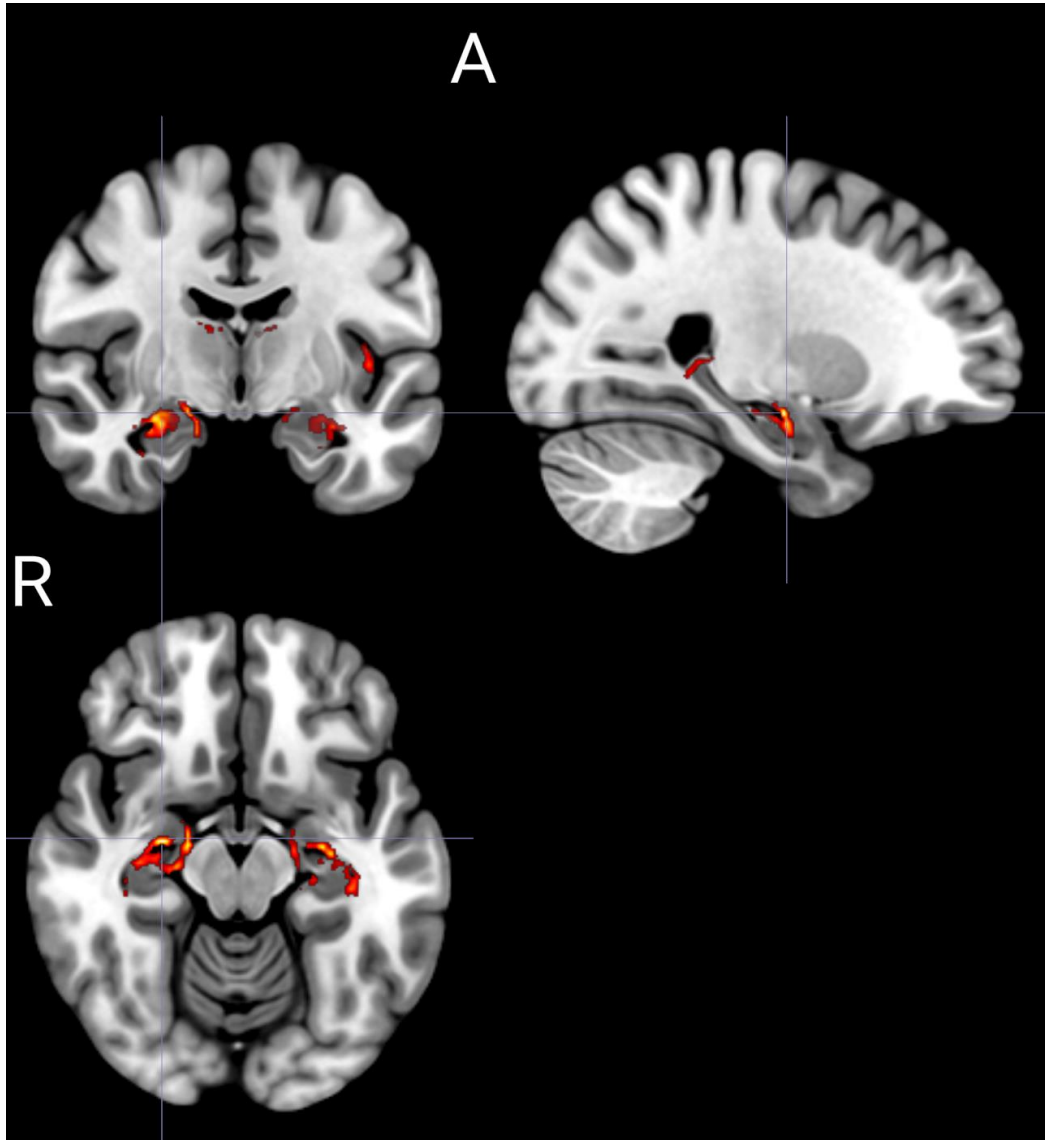
table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 12.66, p = 0.001 (1.000)
Extent threshold: k = 100 voxels, p = 0.264 (0.991)
Expected voxels per cluster, <k> = 86.513
Expected number of clusters, <c> = 4.67
FWEp: 34.309, FDRp: Inf, FWEc: 1993, FDRc: 1993

Degrees of freedom = [1.0, 39.0]
FWHM = 11.0 9.9 10.1 mm mm mm; 11.0 9.9 10.1 {voxels}
Volume: 912858 = 912858 voxels = 689.3 resels
Voxel size: 1.0 1.0 1.0 mm mm mm; (resel = 1098.45 voxels)

Table of results - AD vs HC - (P<0.001)

Univariate GLM — PET_Vt



Statistics: *p-values adjusted for search volume*

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	F	(Z_E)	p_{uncorr}	
0.000	6	0.000	0.012	8	0.002	0.001	0.108	64.16	6.01	0.000	25 -10 -14
		0.006	0.170	2	0.085	0.001	0.108	64.07	6.01	0.000	14 -10 -21
		0.001	0.032	5	0.011	0.001	0.108	63.74	6.00	0.000	18 -11 -13
		0.015	0.211	1	0.211	0.010	0.355	54.13	5.67	0.000	40 49 22
		0.015	0.211	1	0.211	0.025	0.568	50.10	5.52	0.000	-29 -14 -15
		0.015	0.211	1	0.211	0.026	0.568	49.87	5.51	0.000	-27 -12 -15

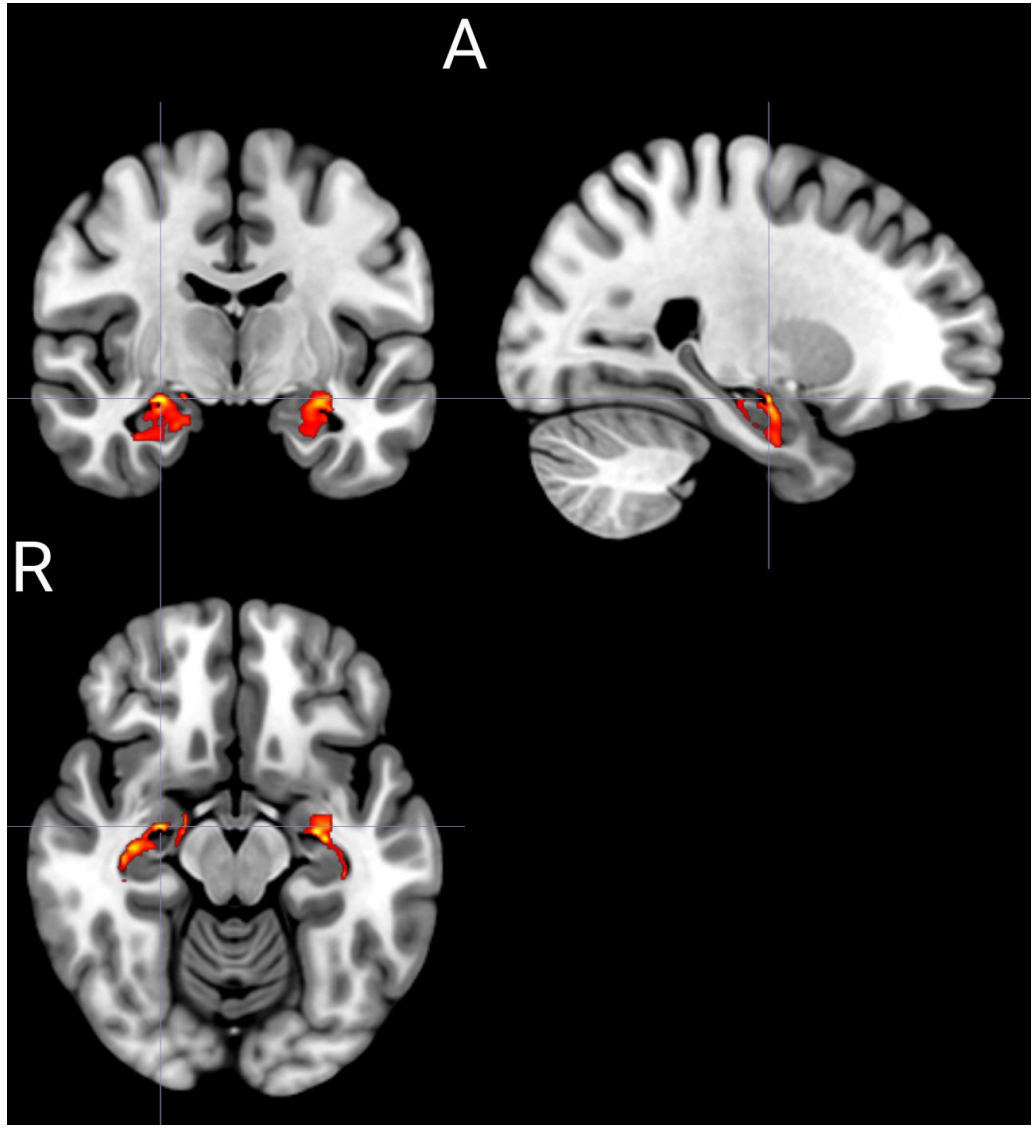
table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 47.00, p = 0.000 (0.050)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 0.686
Expected number of clusters, <c> = 0.07
FWEp: 47.001, FDRp: Inf, FWEc: 1, FDRc: 5

Degrees of freedom = [1.0, 39.0]
FWHM = 4.0 3.9 4.1 mm mm mm; 4.0 3.9 4.1 {voxels}
Volume: 1477777 = 1477777 voxels = 21987.7 resels
Voxel size: 1.0 1.0 1.0 mm mm mm; (resel = 63.34 voxels)

Table of results - AD vs HC - (P<0.05 FWE)

Multivariate GLM — MSPM



Statistics: *p-values adjusted for search volume*

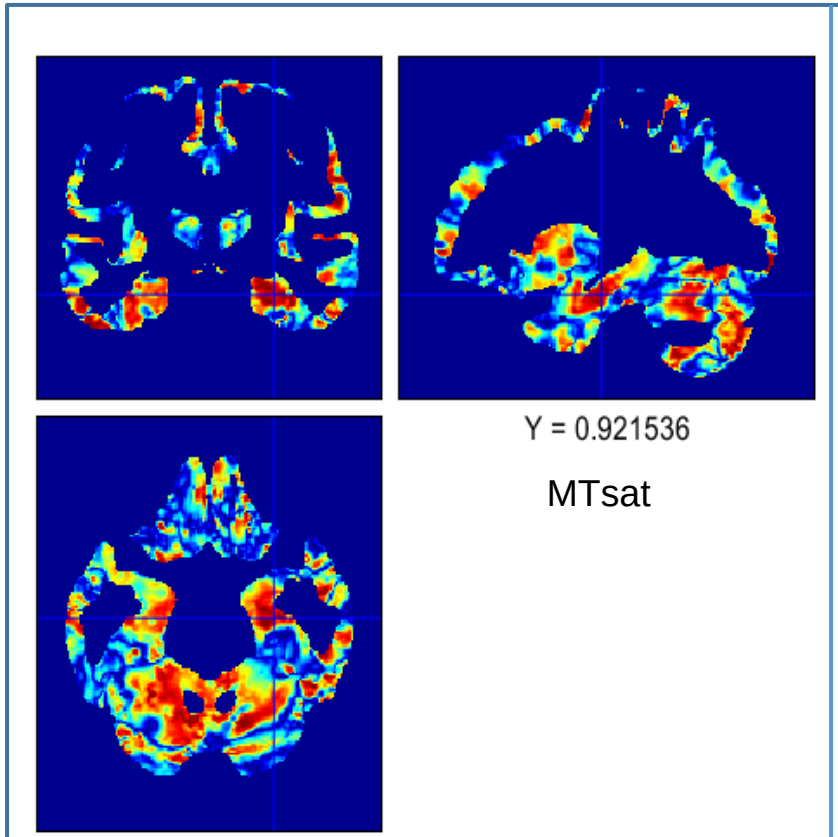
set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	F	(Z_E)	p_{uncorr}			
0.000	10	0.022	0.810	8	0.430	0.005	0.438	21.11	5.37	0.000	25	-10	-14
		0.018	0.810	11	0.353	0.005	0.438	21.00	5.36	0.000	-27	-12	-15
		0.027	0.810	5	0.540	0.026	0.998	17.65	5.00	0.000	35	-18	-13
		0.041	0.810	1	0.810	0.028	0.998	17.51	4.99	0.000	40	49	22
		0.041	0.810	1	0.810	0.037	0.998	16.99	4.92	0.000	37	52	25
		0.041	0.810	1	0.810	0.040	0.998	16.80	4.90	0.000	35	-16	-15
		0.041	0.810	1	0.810	0.045	0.998	16.59	4.88	0.000	-62	-44	35
		0.041	0.810	1	0.810	0.046	0.998	16.55	4.87	0.000	30	-7	-22
		0.041	0.810	1	0.810	0.047	0.998	16.51	4.87	0.000	8	34	-27
		0.041	0.810	1	0.810	0.050	0.998	16.40	4.85	0.000	38	-25	-12

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 16.40, p = 0.000 (0.050)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 13.738
Expected number of clusters, <c> = 0.05
FWEp: 16.397, FDRp: Inf, FWEc: 1, FDRc: Inf

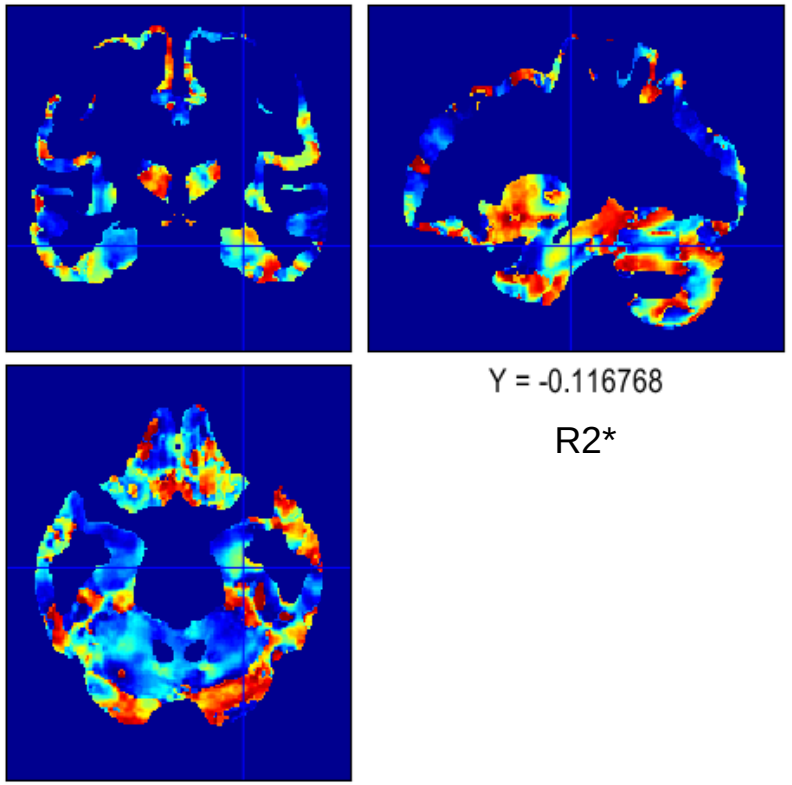
Degrees of freedom = [3.0, 37.0]
FWHM = 11.0 9.9 10.1 mm mm mm; 11.0 9.9 10.1 {voxels}
Volume: 816797 = 816797 voxels = 689.3 resels
Voxel size: 1.0 1.0 1.0 mm mm mm; (resel = 1098.45 voxels)

Table of results - AD vs HC - (P<0.05 FWE)



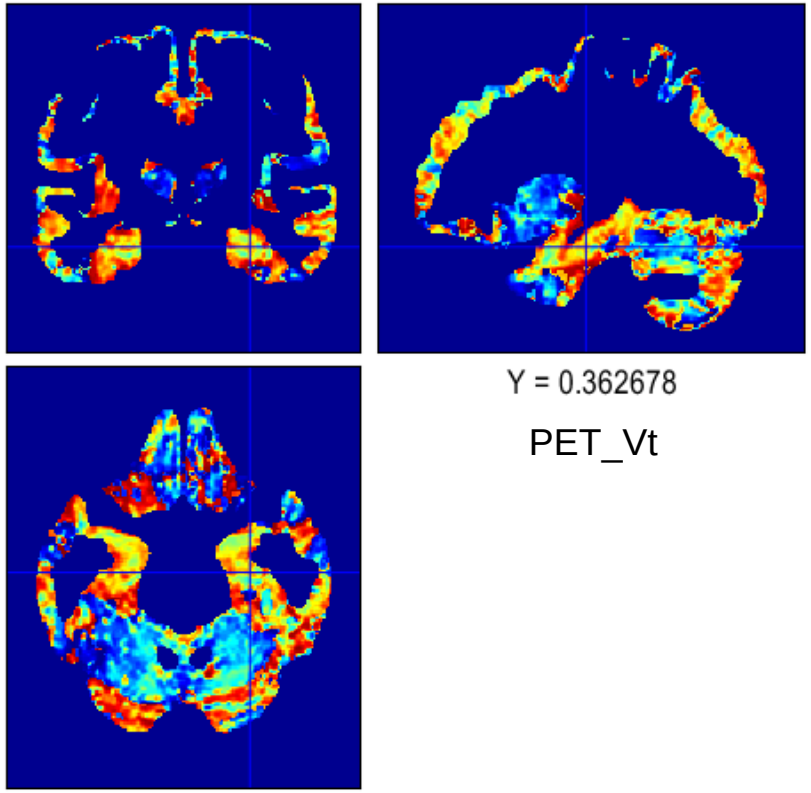
Y = 0.921536

MTsat



Y = -0.116768

R2*



Y = 0.362678

PET_Vt

Take home message:

- Quantitative maps can be used to assess AD in its early stages.
- Alteration in **myelin content** and **synaptic density** in early AD occurs in the hippocampus.
- Accounting for the interactions between myelin, iron, and SV2A protein we can get a more accurate characterization of the difference between the groups of AD and HC.
- **Multivariate GLM model** is preferable to multiple univariate models to test for AD, which relies on a cascade of processes.

THANK YOU!

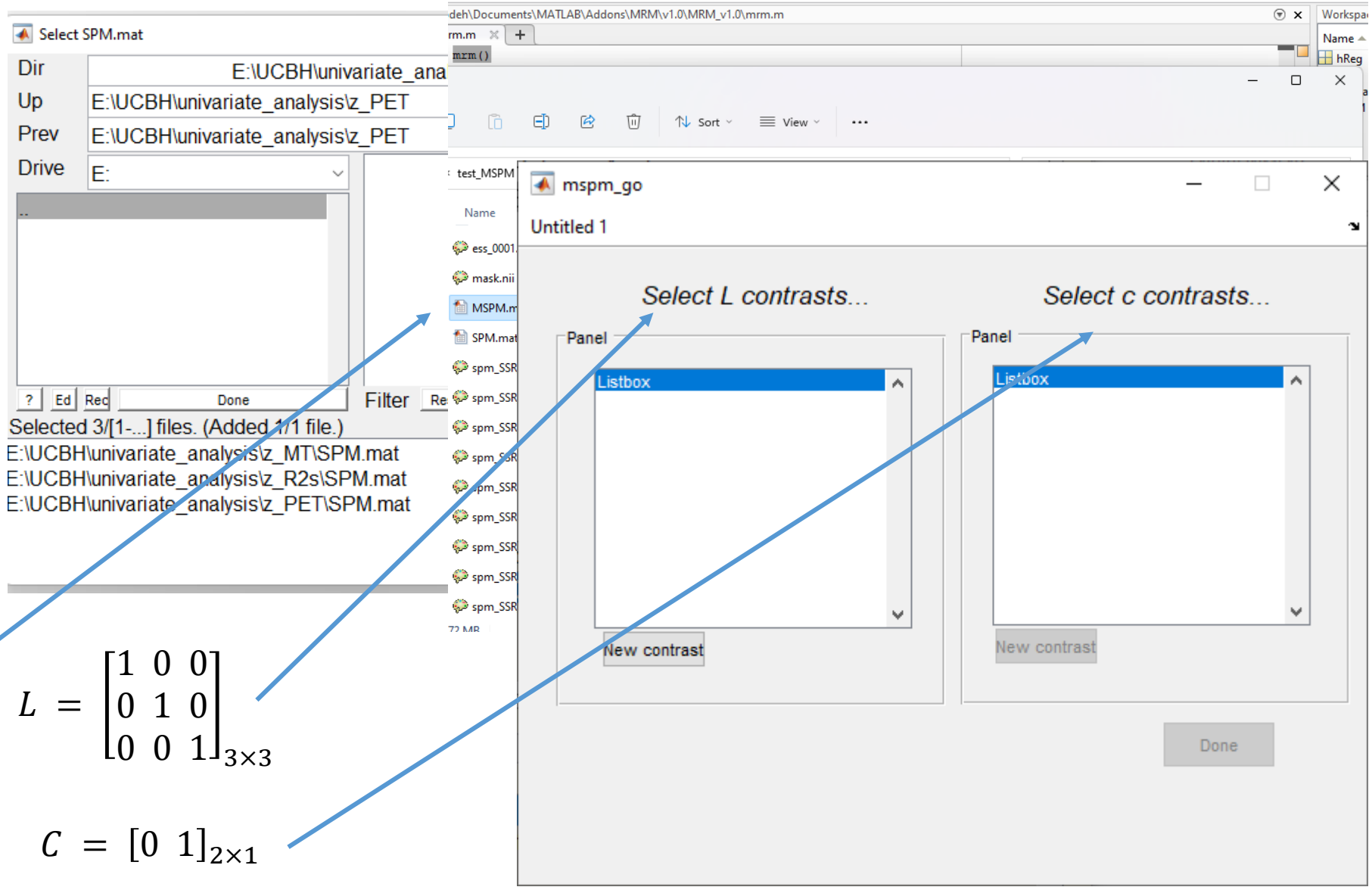
https://hdl.handle.net/2268/296010

Cluster number	Coordinate at peak	F-Value at peak	Cluster P-value*	Cluster size	Brain region
Mtsat(P<0.001 FWE uncorrected at voxel level analysis)					
1	(28 –7 –27)	26.58	0.002	1993	Right hippocampus
PET_vt (P<0.05 FWE corrected at voxel level analysis)					
1	(25,-10,-14)	64.16	0.000	8	Right hippocampus
2	(14,-10,-21)	64.07	0.006	2	Right hippocampus
3	(18,-11,-13)	63.74	0.001	5	Right amygdala
Multimodal (P<0.05 FWE corrected at voxel level analysis)					
1	(25,-10,-14)	21.11	0.022	8	Right hippocampus
2	(-27,-12,-15)	50.10	0.018	11	Left hippocampus
3	(35,-18,-13)	34.02	0.027	5	Right hippocampus

MSPM toolbox:

Example :

- **Three modalities**
- **43 subjects**
- **Two groups**



$$X = \begin{bmatrix} AD_{MT} & AD_{MT} \\ AD_{R2s} & AD_{R2s} \\ AD_{PET} & AD_{PET} \\ HC_{MT} & HC_{MT} \\ HC_{R2s} & HC_{R2s} \\ HC_{PET} & HC_{PET} \end{bmatrix}_{43\times 2}$$

$$L = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}_{3\times 3}$$

$$C = [0 \ 1]_{2\times 1}$$