Principal components, autoencoder and glioblastoma

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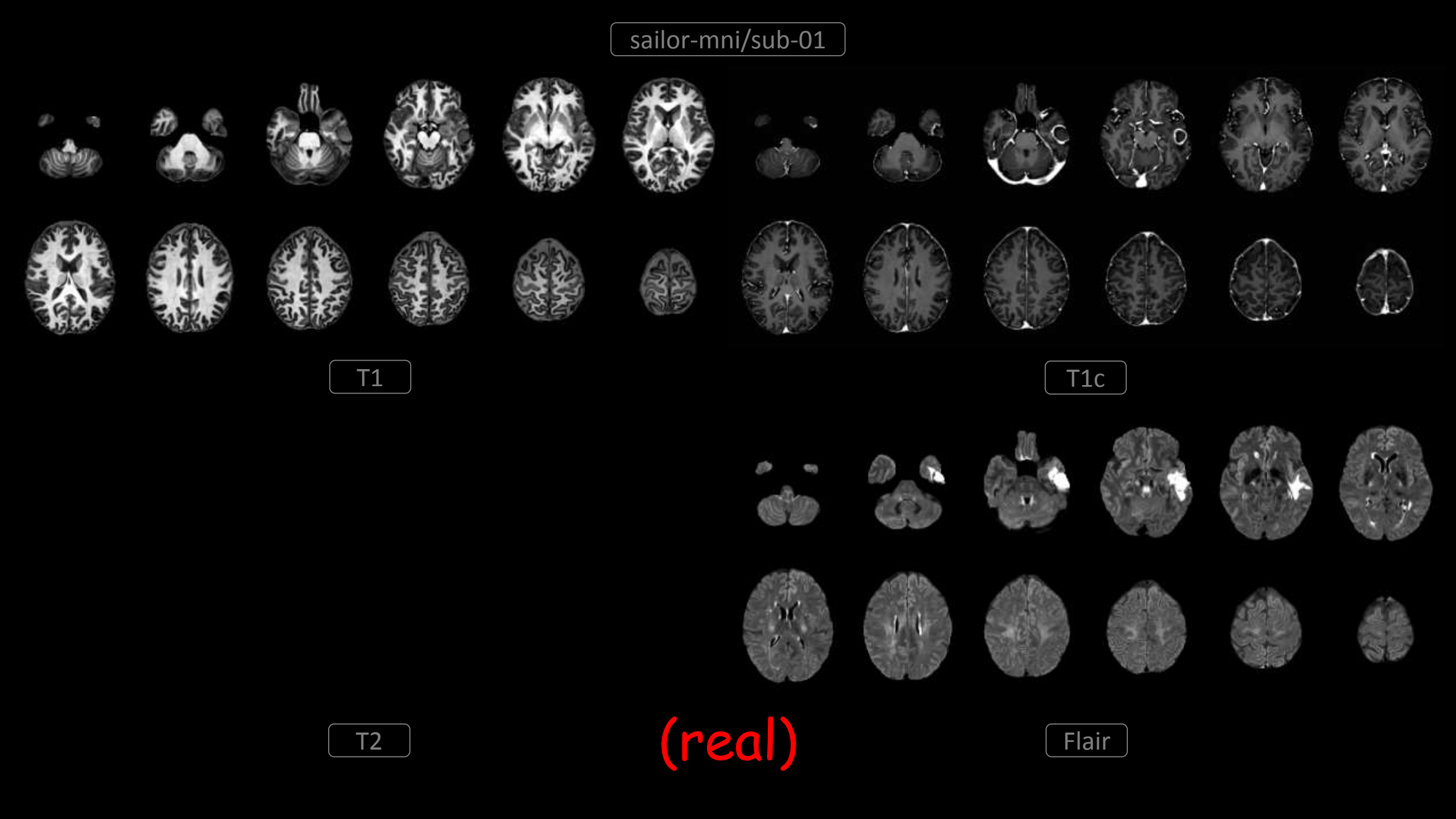
Outline

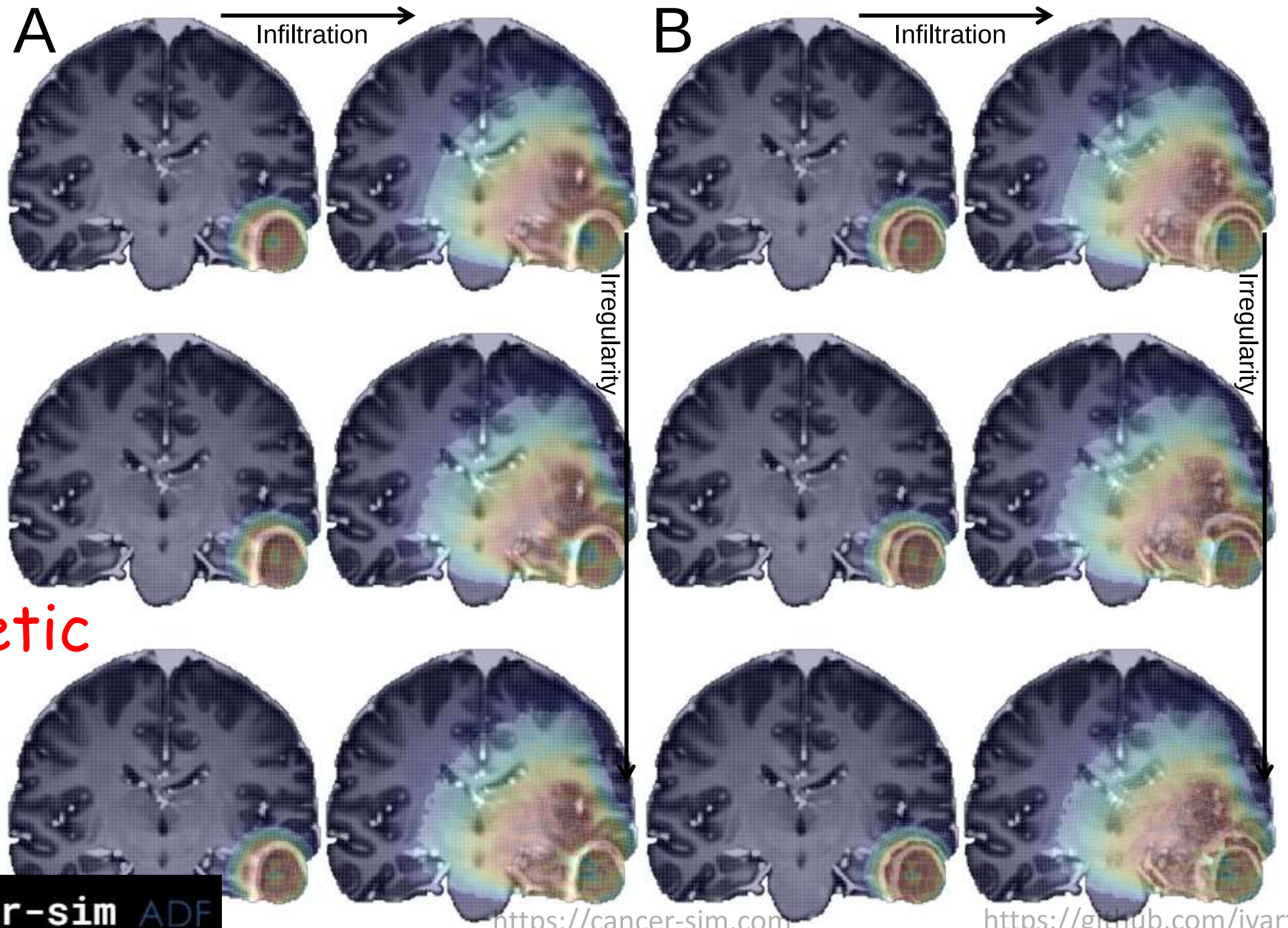
- Data: Longitudinal MRI of glioblastoma[1] (post operative and during treatment)
  - Surgery, chemotherapy and radiotherapy (Supp regimen[2])
- Hypotheses
- Principal Component Analysis
- Autoencoder
- Summary & Conclusion

[1]SAILOR: https://www.sciencedirect.com/science/article/pii/S0730725X19305430
[1]ONCOHabitats preprocessing: https://doi.org/10.1016/j.ijmedinf.2019.05.002
[2]https://www.nejm.org/doi/full/10.1056/NEJMoa043330

Data


sailor-mni/sub-01
T1
T1c
T2
(real)
Flair

Synthetic growth model



A: 3 mm
B: 8 mm

synthetic

cancer-sim ADF

https://cancer-sim.com

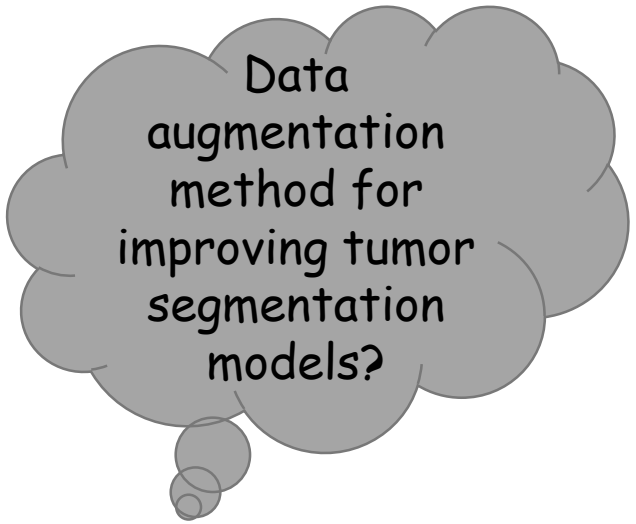
https://github.com/ivartz/cancer-sim

„irregularity“

„infiltration“

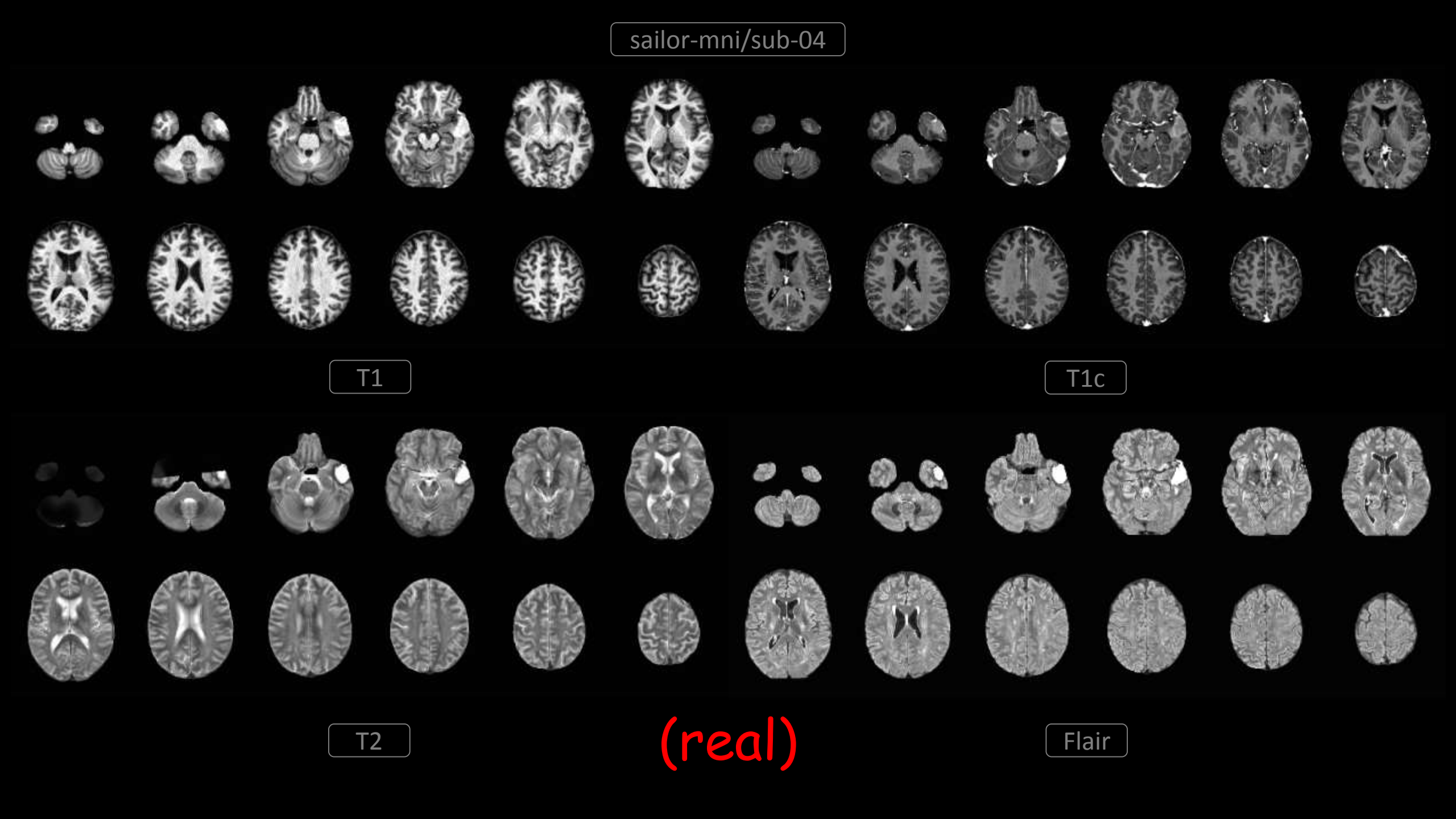
„displacement“

```
29  # Perlin max and min resolution
30  presmin=0.03
31  presmax=0.05
32  presres=2
33
34  # Perlin noise maximum magntude (in absolute vector magnitude value)
35  pabsmin=0
36  pabsmax=0.6
37  pabsres=2
38
39  # Min and max brain coverage x and resolution
40  # x=1-y, y element [0,1]; 0=largest brain coverage
41  minbc=0.1
42  maxbc=1
43  resbc=2
44
45  # Min and max displacement magnitude and resolution
46  mindisp=3
47  maxdisp=8
48  resdisp=2
```



https://github.com/ivartz/cancer-sim-search/blob/main/grid-search-3d.sh

more data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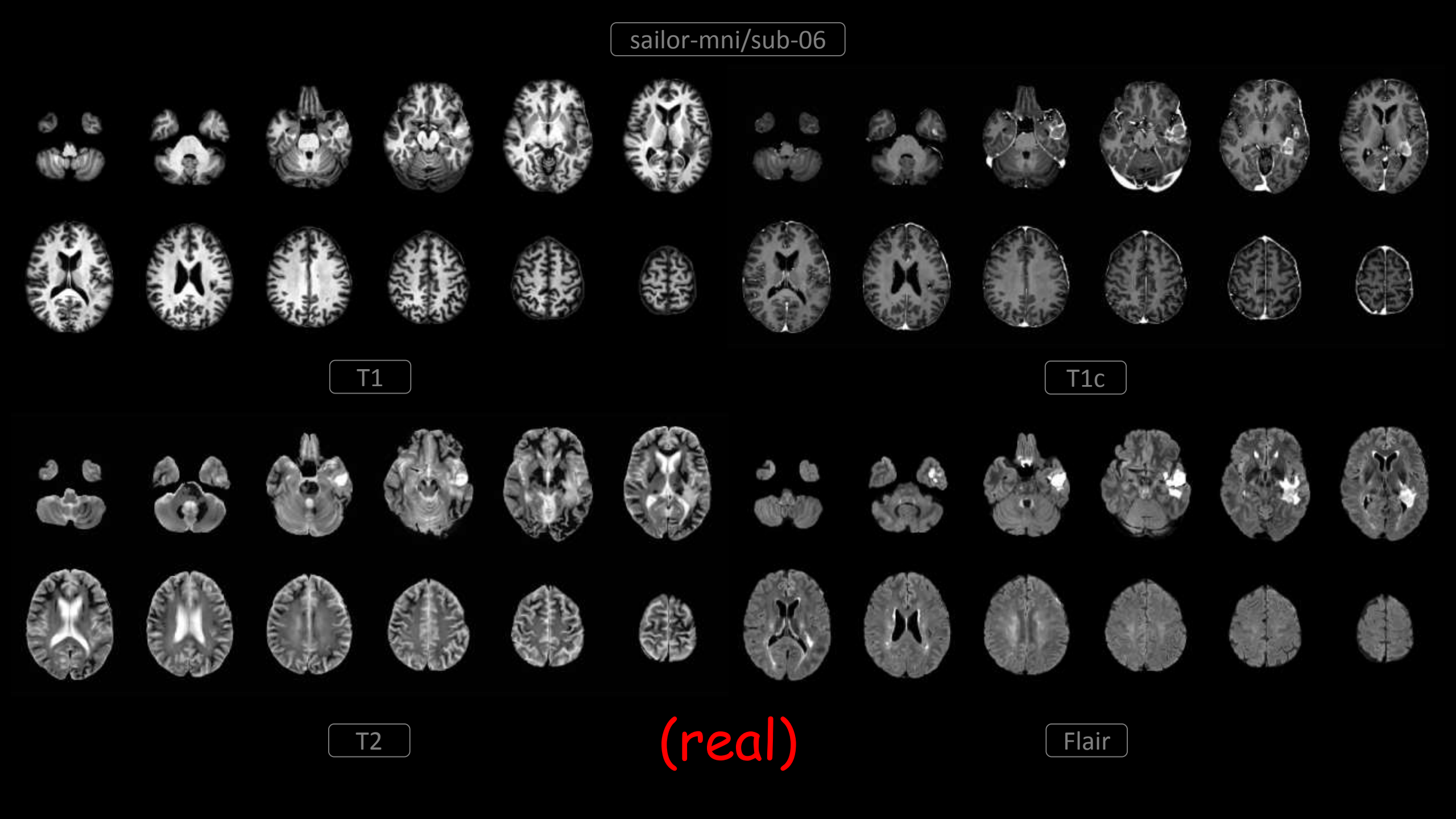
T1
T1c
T2
(real)
Flair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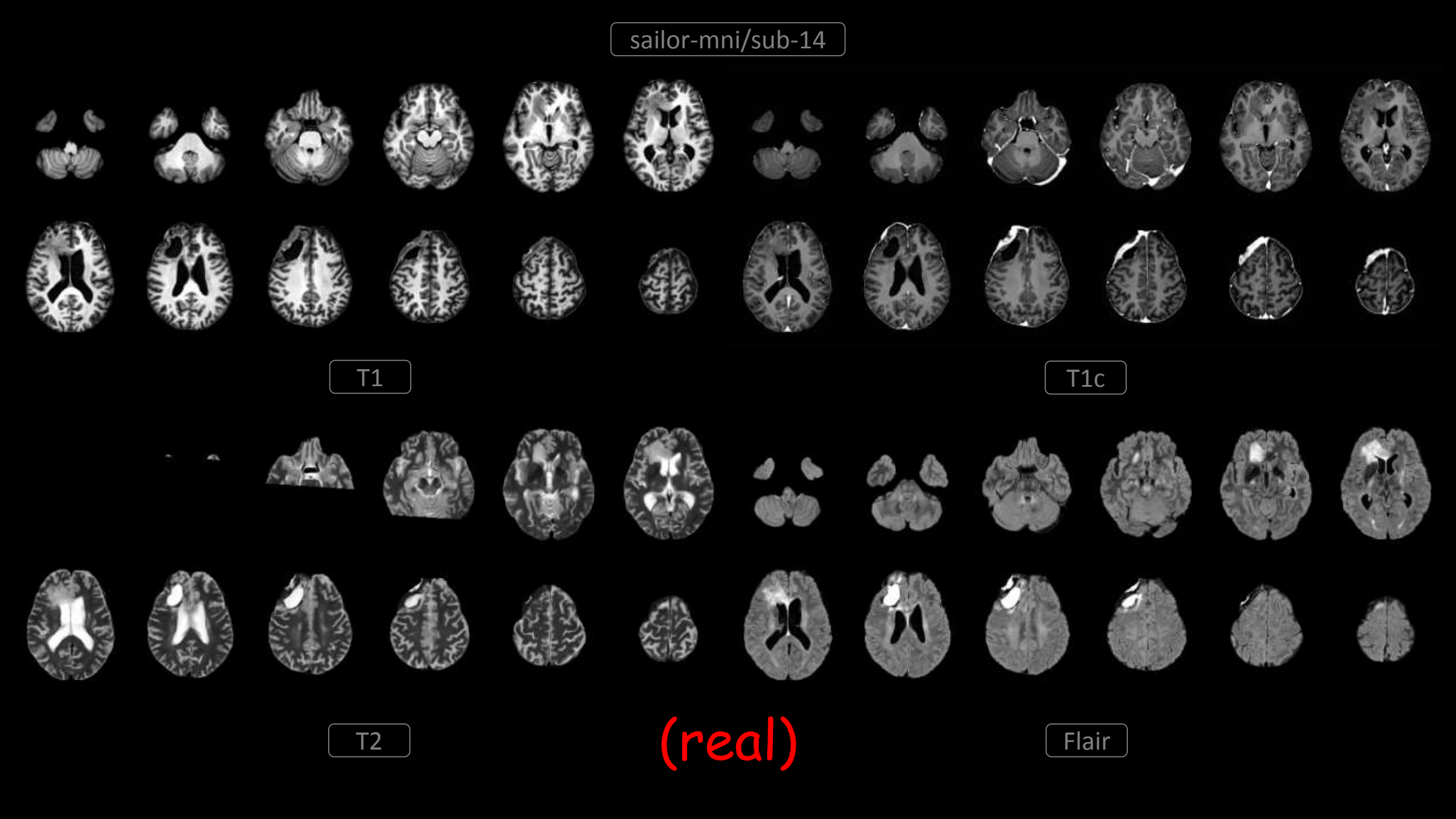
T1
T1c
T2
(real)
Flair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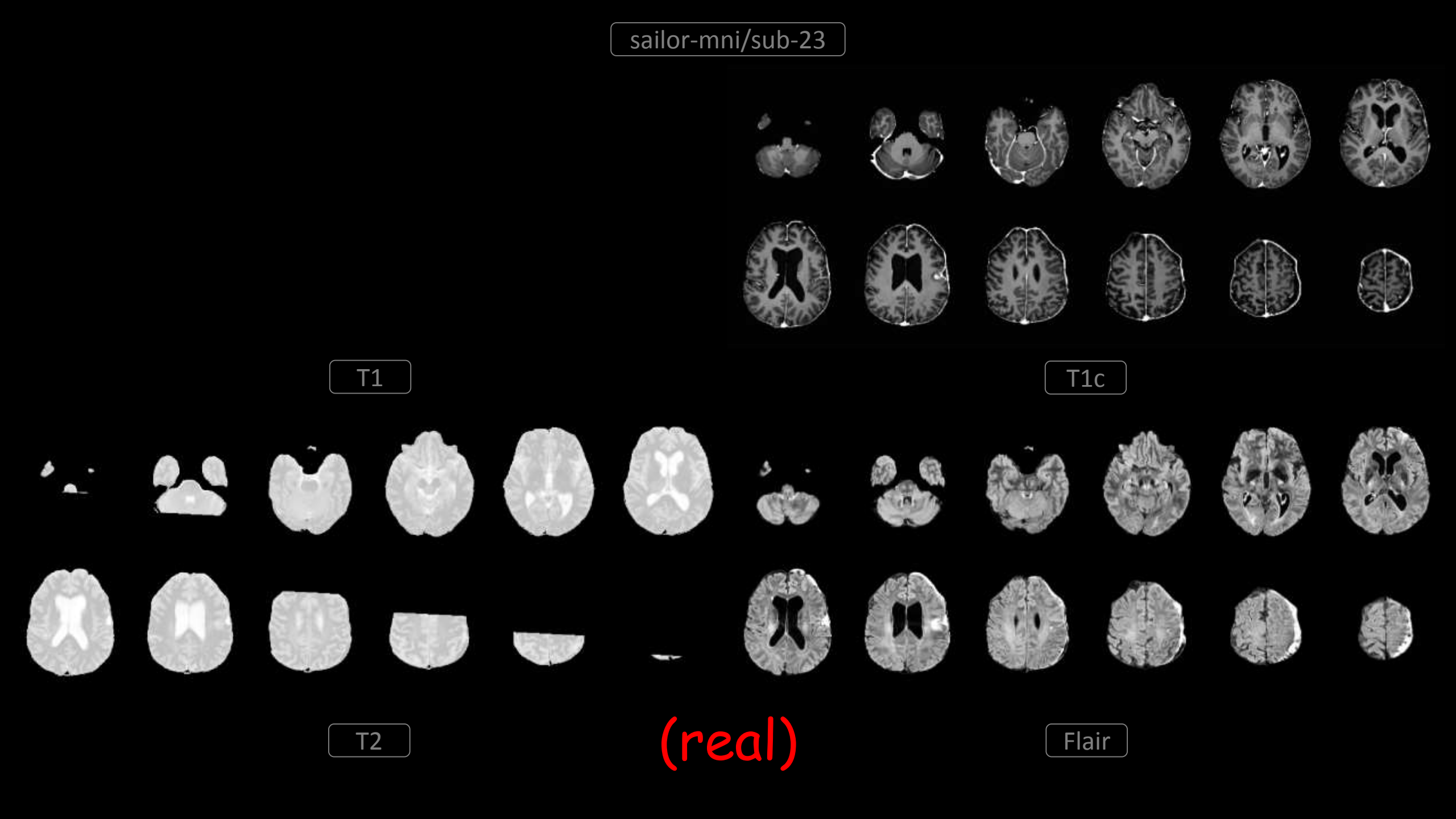
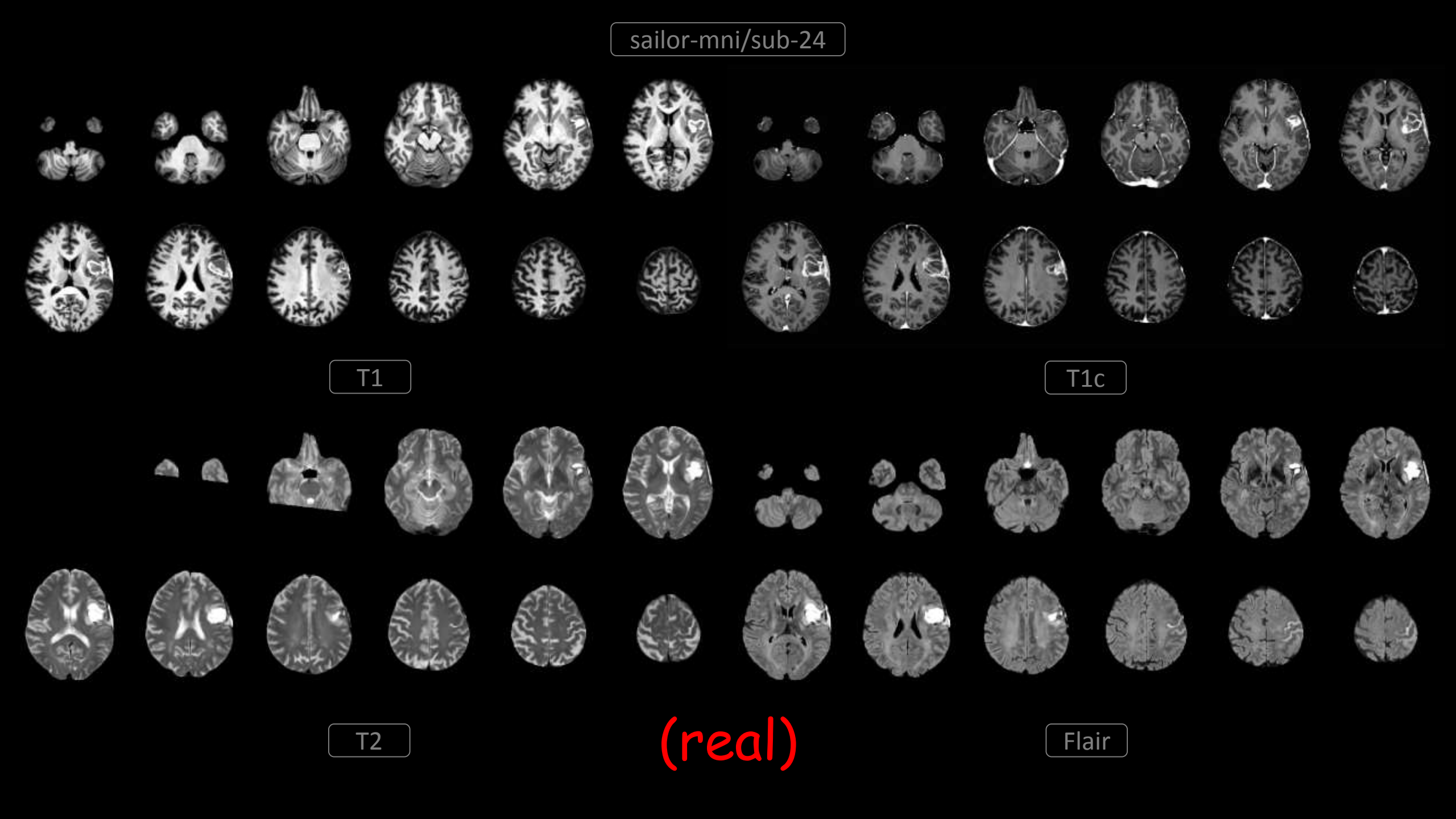
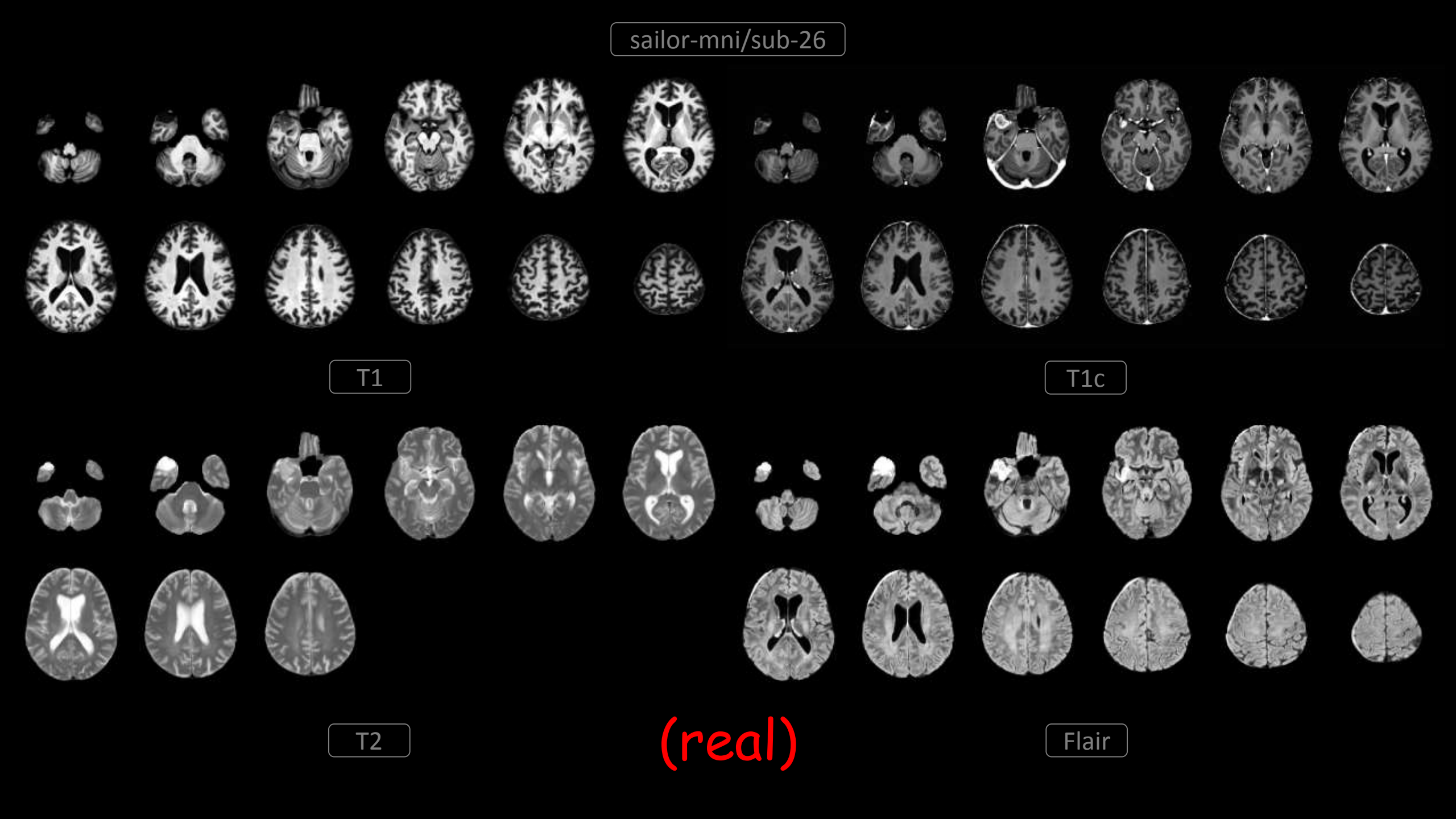
T1
T1c
T2
(real)
Flair


sailor-mni/sub-23
T1
T1c
T2
Flair
(real)


sailor-mni/sub-24
T1
T1c
T2
(real)
Flair


sailor-mni/sub-26
T1
T1c
T2
(real)
Flair

Hypotheses

Claims to verify & purpose of analyses

Hypotheses

1. Ventricle change across time is one of the most stable temporal patterns in longitudinal MRI of glioblastoma
2. Mean ventricle change across multiple subjects consists of ventricle volume increase
3. Ventricle change as temporal pattern can be correlated with clinical parameters for useful predictions

Clinical parameters (any suggestions?)

- Response assessment in neuro-oncology[1] (RANO; 1-4) (one exam to the next)
- Overall survival (months): Glioblastoma median OS of 12-15 months[2]
- MGMT promoter methylation status (yes/no): higher OS for yes (21 vs. 14)[3]
- IDH status (mutant/wildtype): wildtype has worst OS (10 vs. 24)[4]
- Use of steroids (Yes: to reduce pressure)
- Change of ventricle volume vs. tumor volume
- Change of ventricle volume vs. tumor growth

- Ventricles to predict progression vs. pseudo-progression: Changes in image caused by treatment vs. caused by cancer progression

[1]https://www.neuroradiologi.dk/onewebmedia/Updated%20RANO.pdf
[2]https://www.nejm.org/doi/full/10.1056/nejmra0708126
[3]https://oncologypro.esmo.org/education-library/factsheets-on-biomarkers/mgmt-promoter-methylation-in-glioma
[3]https://ascopubs.org/doi/abs/10.1200/jco.2011.29.15_suppl.2006
[4]https://www.ncbi.nlm.nih.gov/books/NBK469981/table/chapter2.t1/

Preliminaries

Data matrix $X = \begin{bmatrix} a_{11} & \cdots & a_{1N} \\ \vdots & \ddots & \vdots \\ a_{M1} & \cdots & 1_{MN} \end{bmatrix} = [x_1 \cdots x_N] \in \mathbb{R}^{M\,(samples)xN(variables)}$

Mean of variable $\hat{x} = \frac{1}{M}\sum_{i=1}^{M} x_i$

Variance of variable $var(x) = \frac{1}{M-1}\sum_{i=1}^{M}(x_i - \hat{x})^2$ Standard deviation of variable $std(x) = \sqrt{var(x)}$

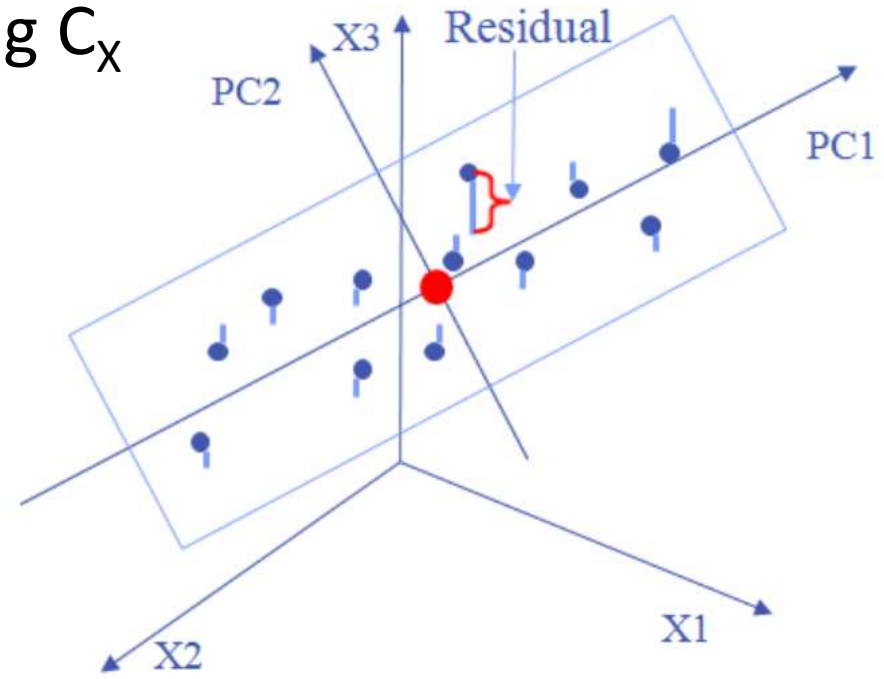
Covariance between variables $cov(x_1, x_2) = \frac{1}{M-1}\sum_{i=1}^{M}(x_{1i} - \hat{x}_1)(x_{2i} - \hat{x}_2)$

Covariance matrix of X $C_X = \frac{1}{M-1}X^T X \in \mathbb{R}^{NxN}$

Principal Component Analysis (PCA)

- Traditional dimensionality reduction method
- Describes variation in the data matrix X (M rows, N columns) in terms of $k \leq N$ uncorrelated variables
- Analog to computing C_X

$$X = \begin{bmatrix} x_{11} & \cdots & x_{1N} \\ \vdots & \ddots & \vdots \\ x_{M1} & \cdots & x_{MN} \end{bmatrix}$$



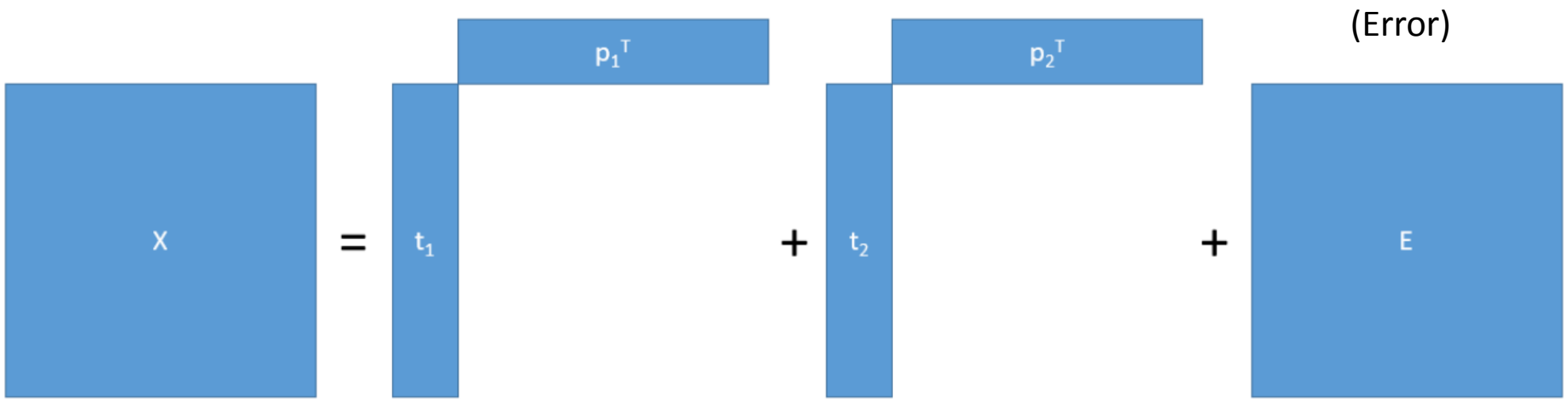
M=12 (samples)
N=3 (variables)
k=2 (reduced variables)

$X = USV^T$ Singular value decomposition

$X = T_k P_k{}^T + E$

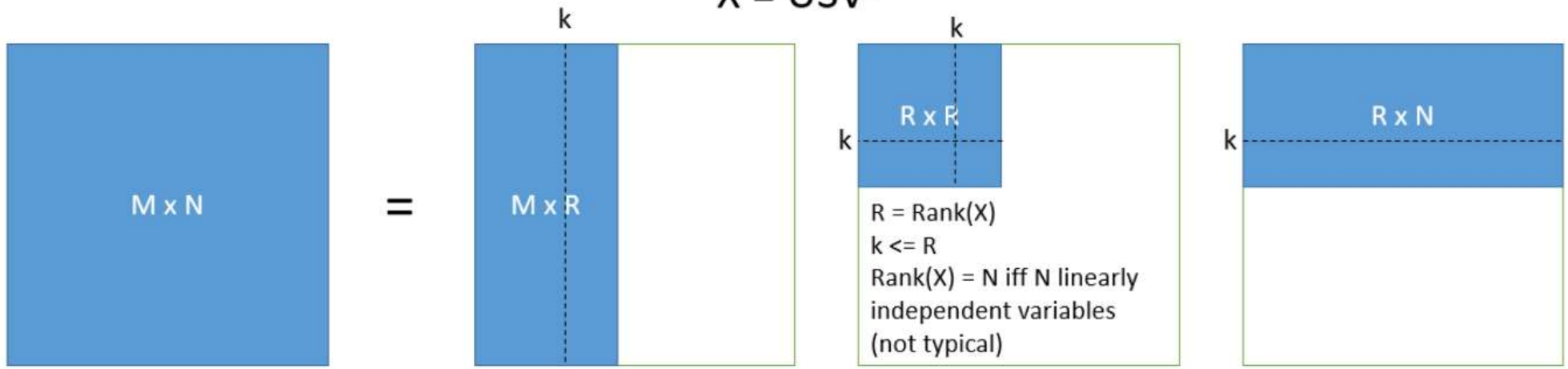
$T_k = UkSk$ “Scores”

$P_k{}^T = V_k{}^T$ “Loadings”: “Variable importance”



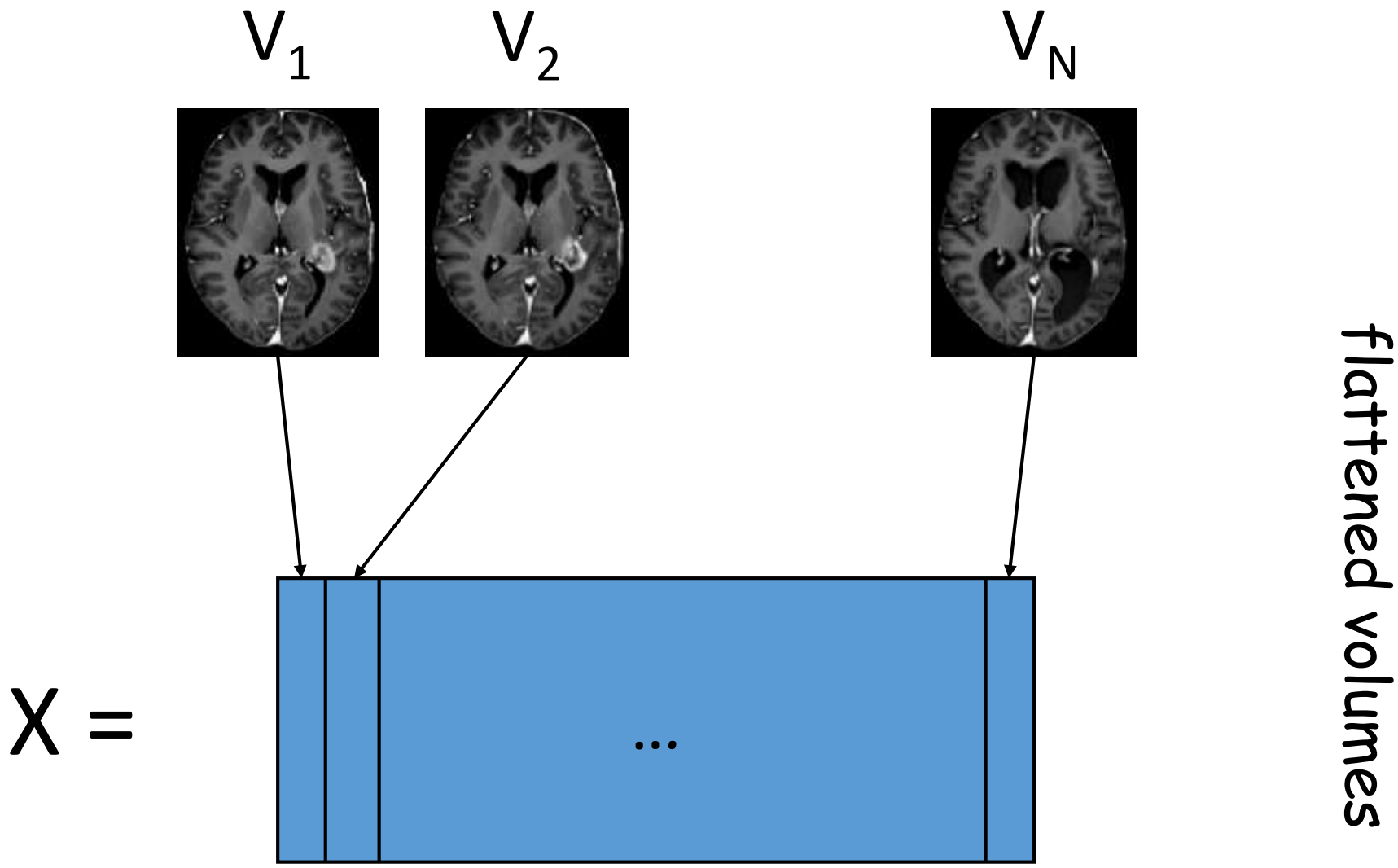
Full

$X = USV^T$



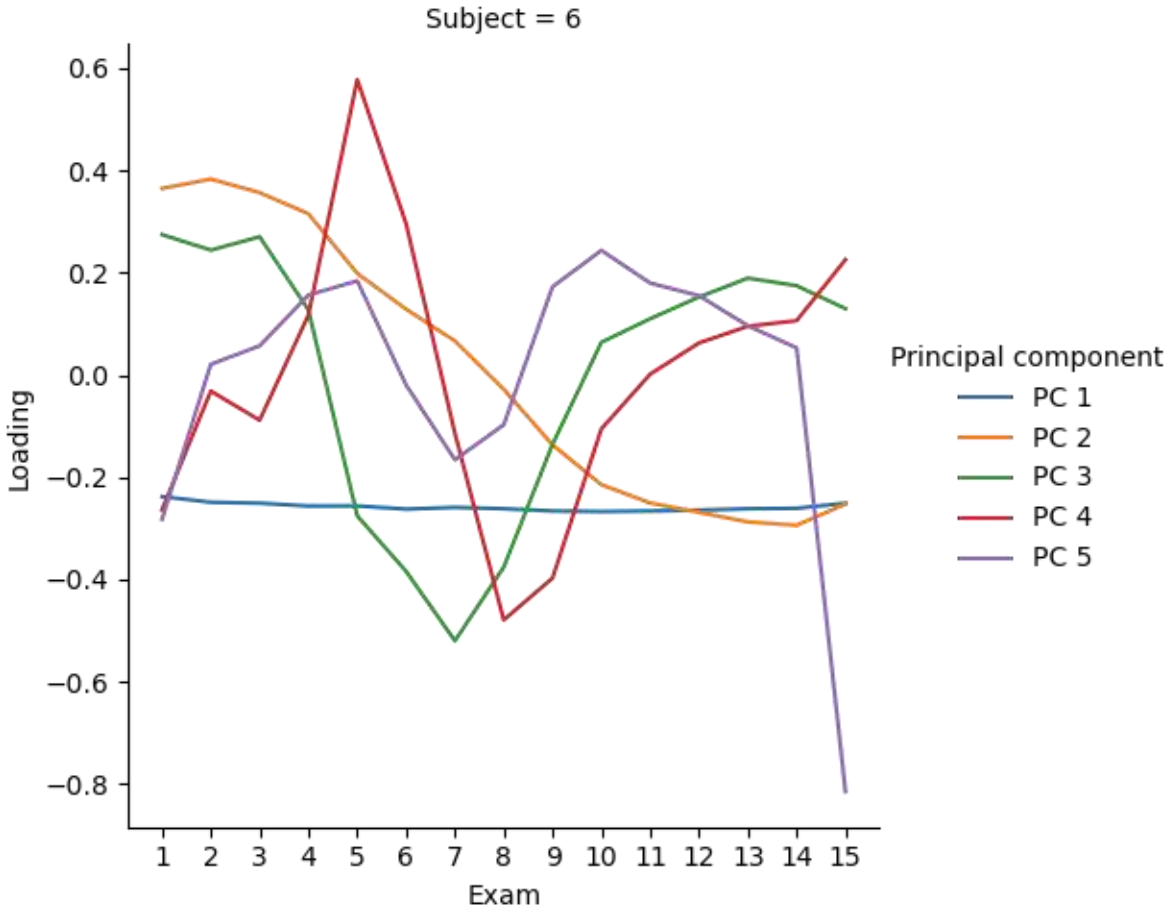
Approximation: Select top k components

$X_k = U_k S_k V_k^T$

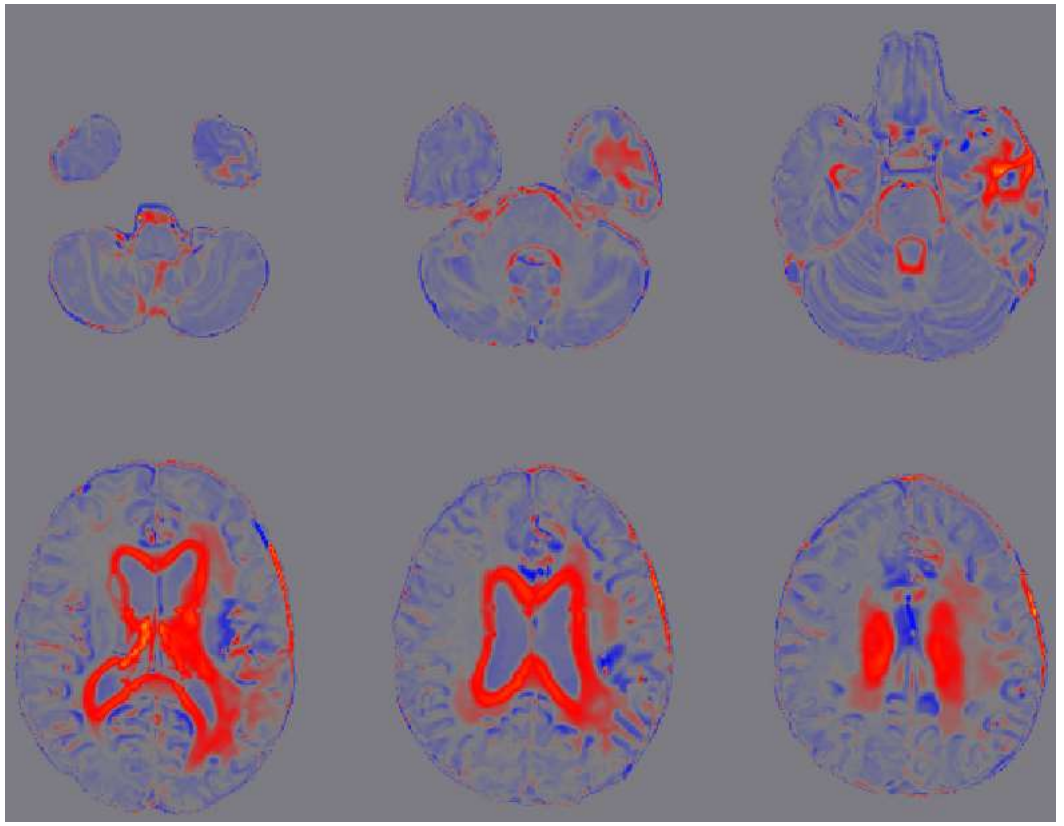


Column order irrelevant!

PCA model of subject 6 (all exams)

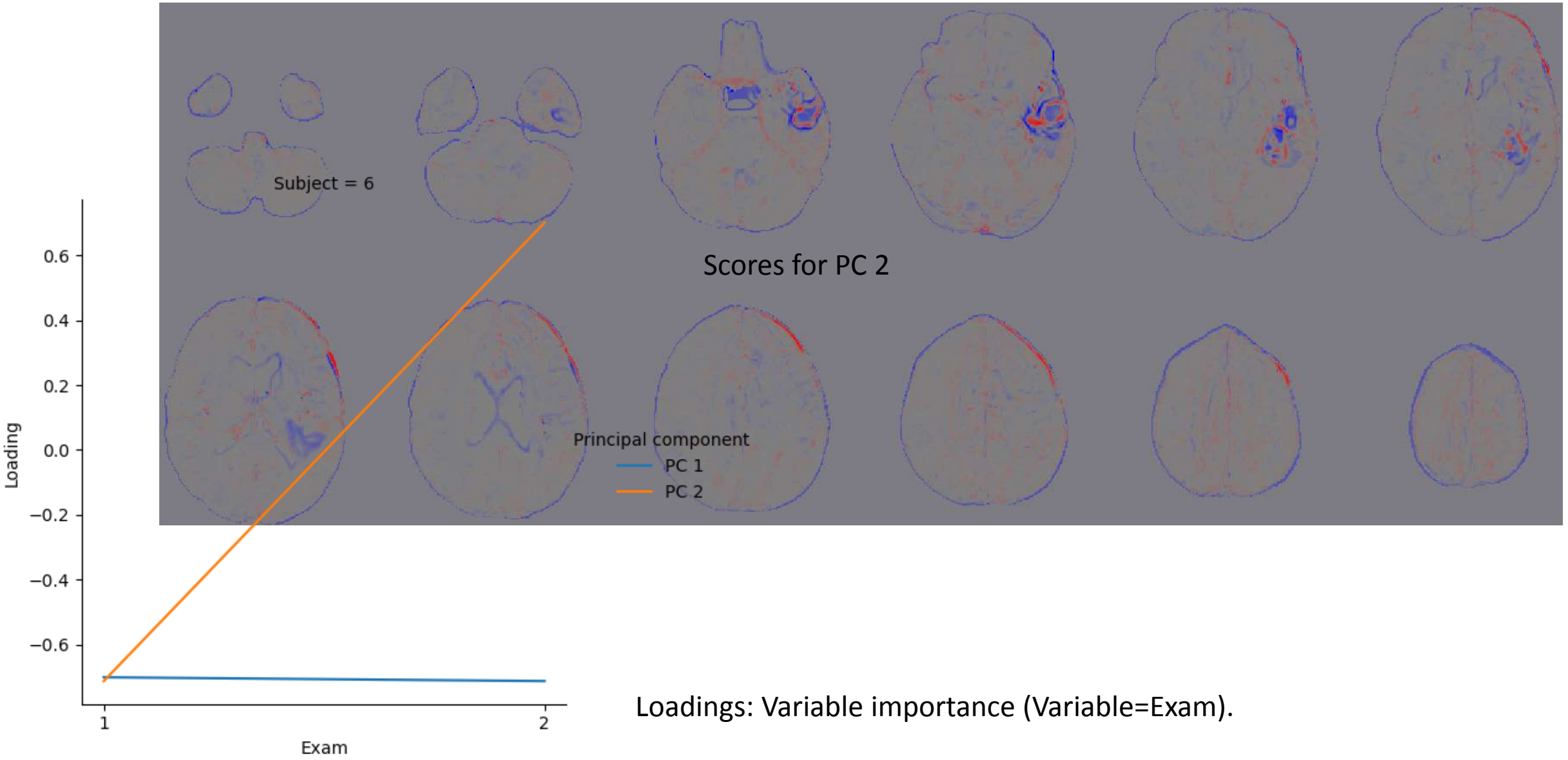


Loadings: Variable importance (Variable=Exam). First exam is the most important (has highest intensities in red regions) for PC 2



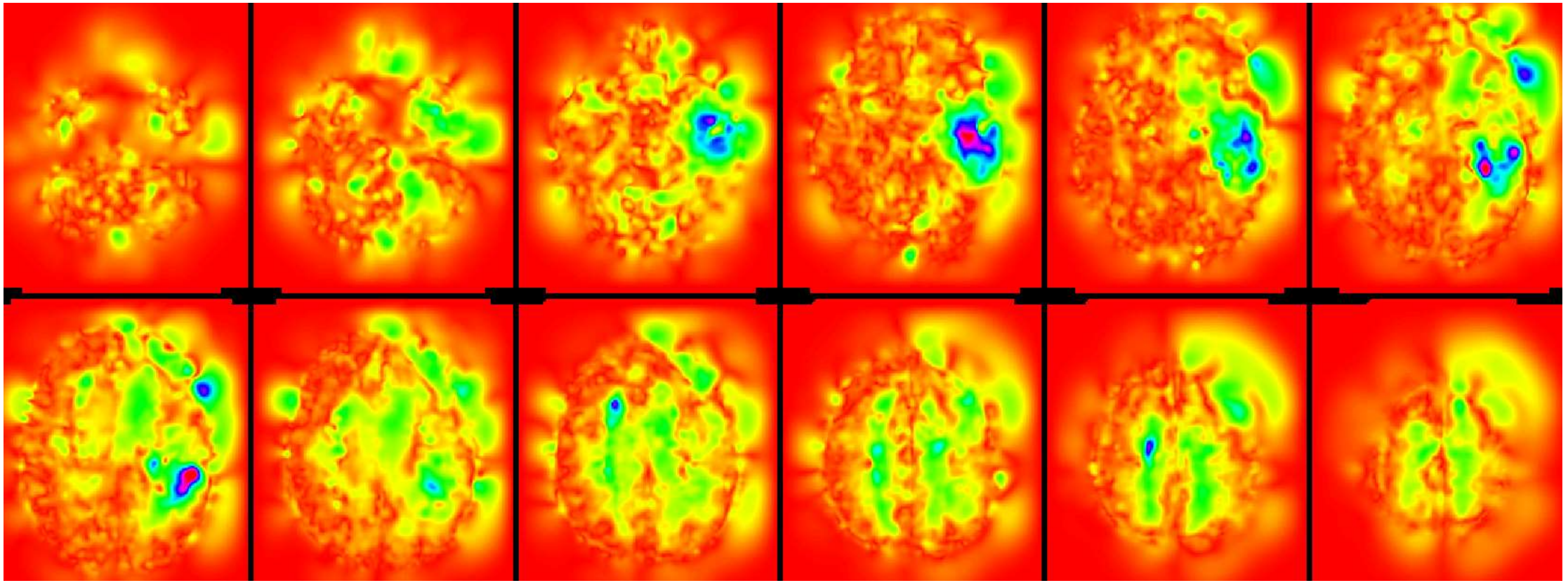
Scores for PC 2. Red regions represent intensity change caused by expanding ventricles. Red and blue represents positive and negative values, respectively

PCA model of subject 6 (first two exams)



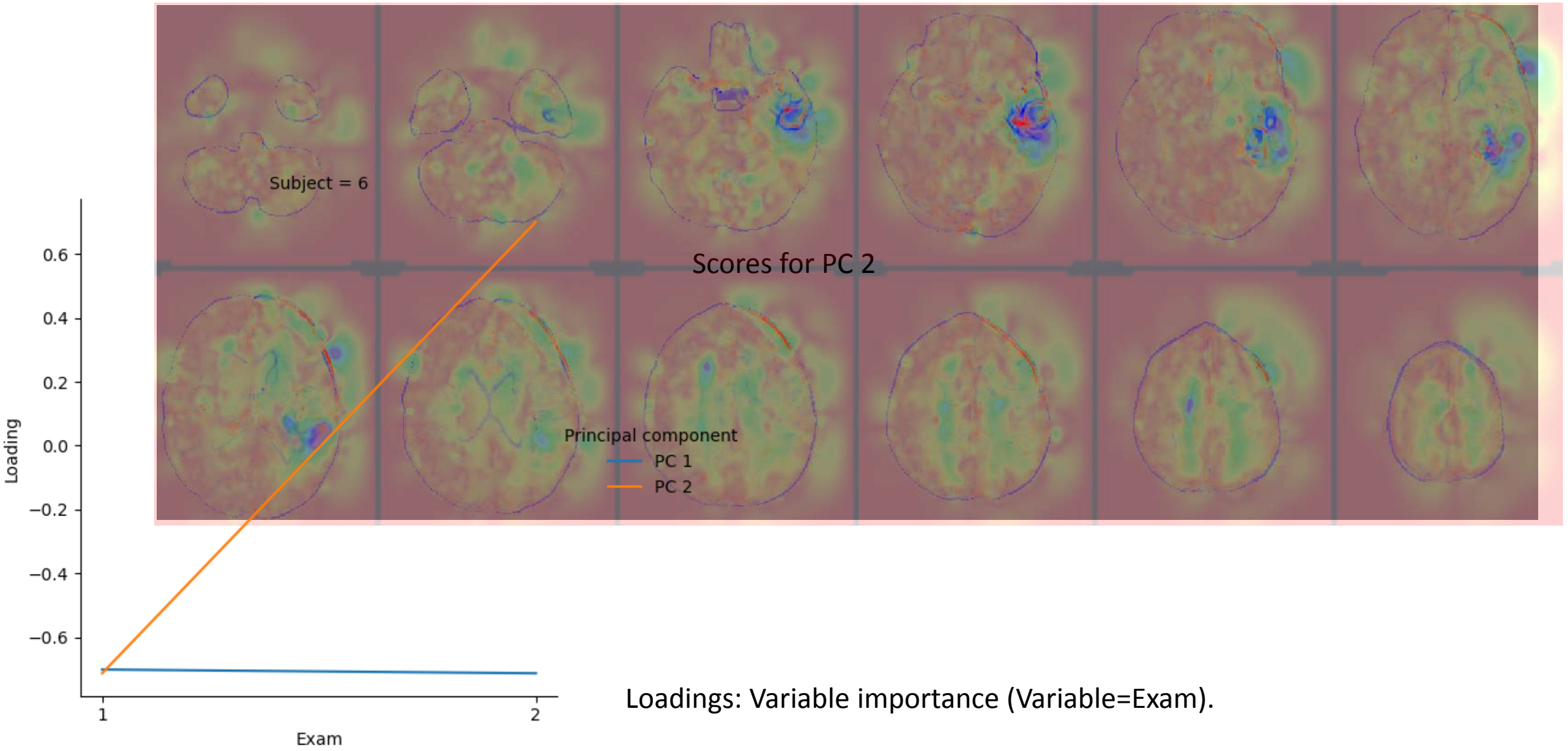
Loadings: Variable importance (Variable=Exam).

Comparison: Estimated displacement in subject 6 (first to second exam)

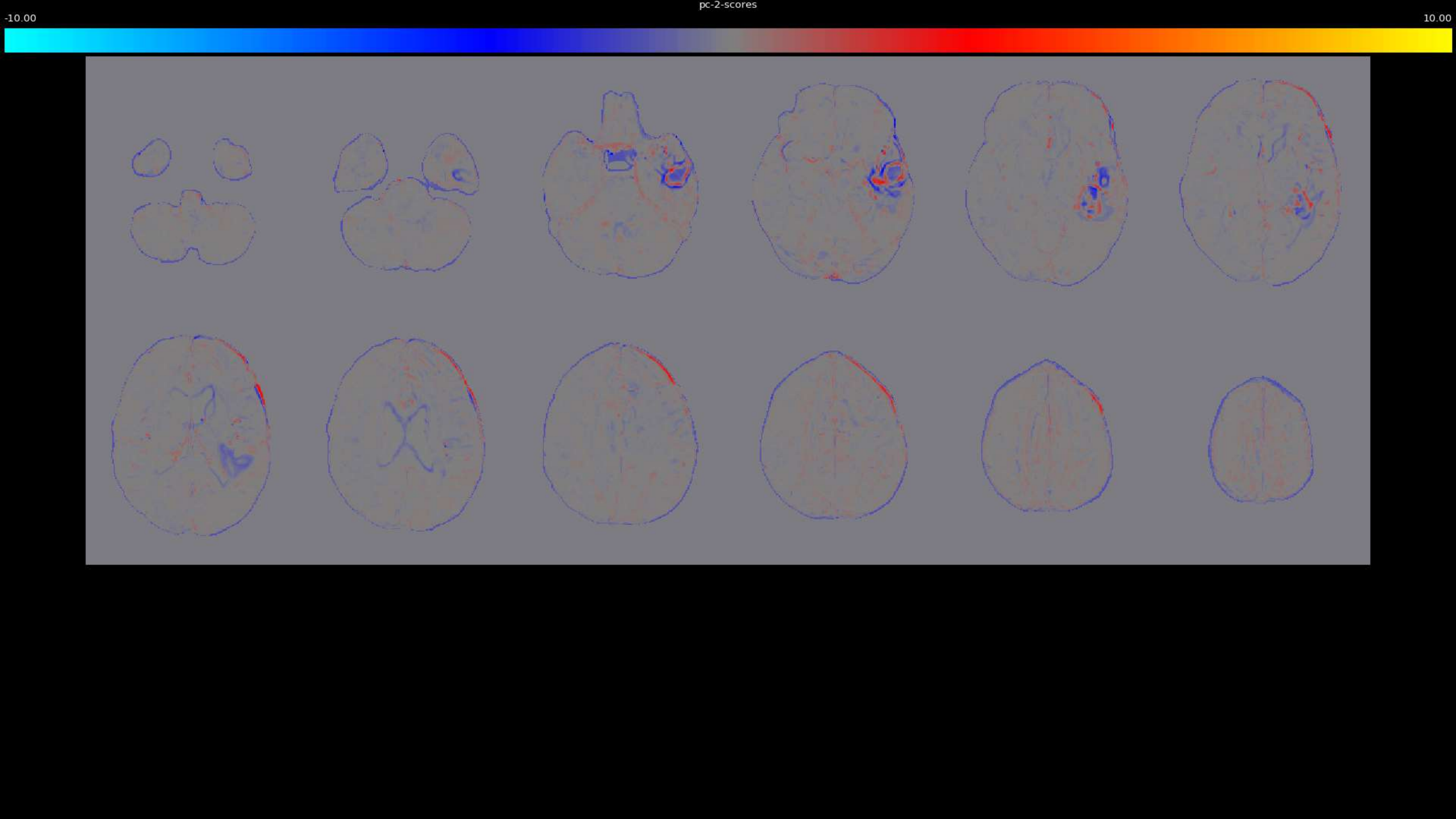


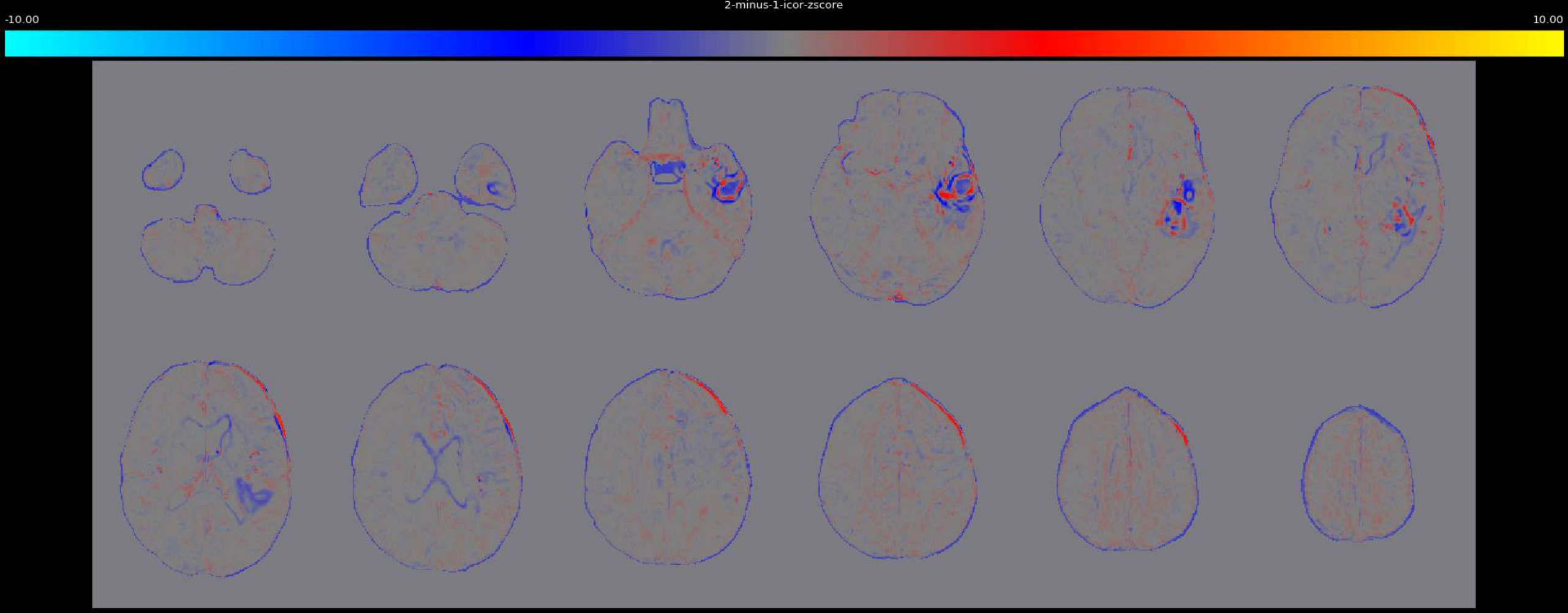
Method: Symmetric diffeomorphic registration with cross-correlation metric (ANTs SyN CC)
https://doi.org/10.1016/j.media.2007.06.004

PCA model of subject 6 (first two exams) with ANTs SyN displacement field overlaid



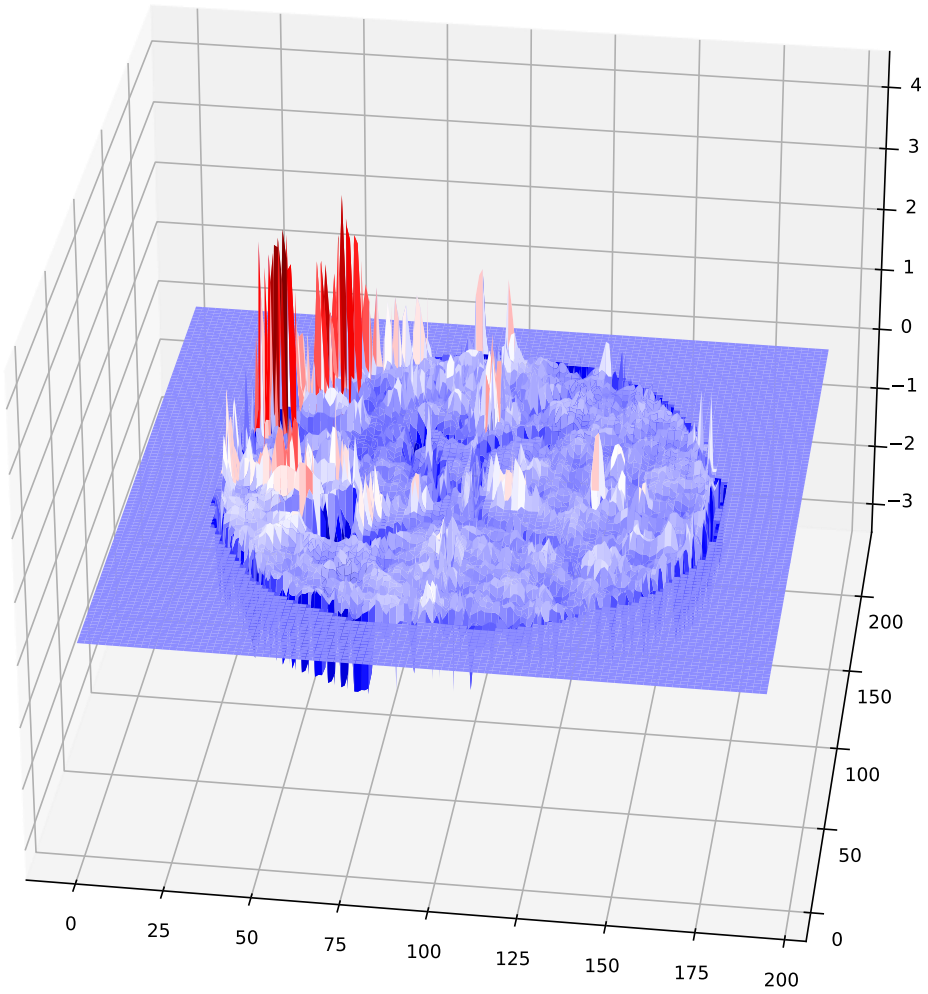
Loadings: Variable importance (Variable=Exam).


pc-2-scores
-10.00
10.00

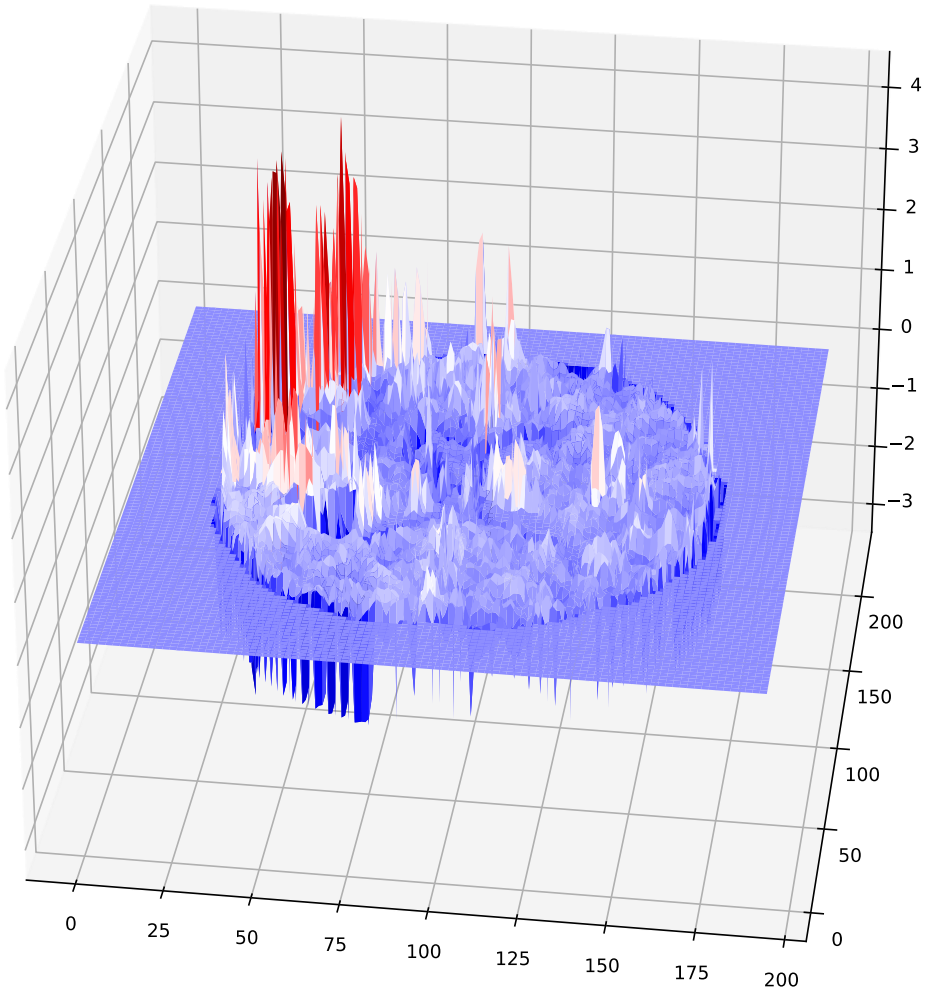

2-minus-1-icor-zscore
-10.00
10.00

PC 2 PCA vs. difference image of two exams

Principal Component 2

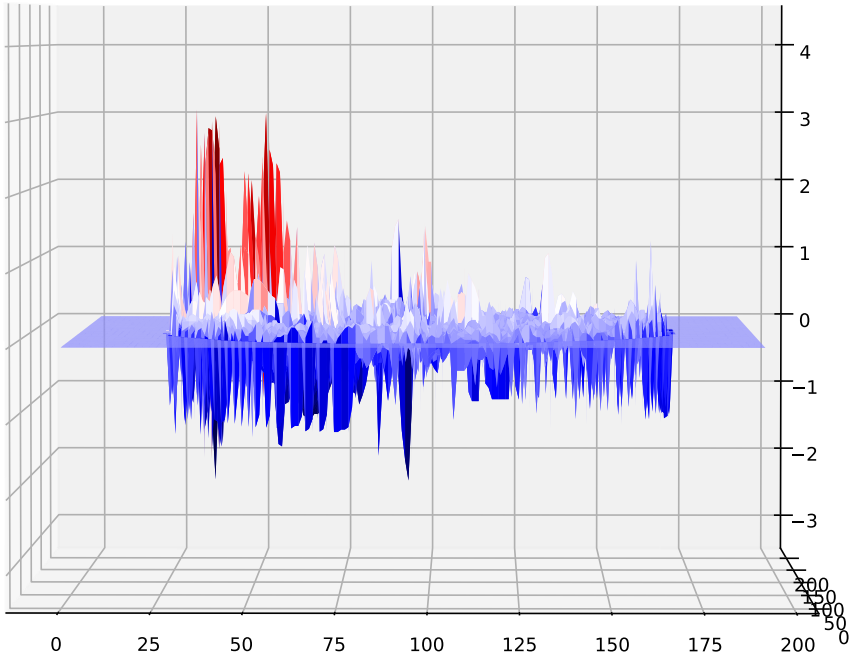


Second - first MRI

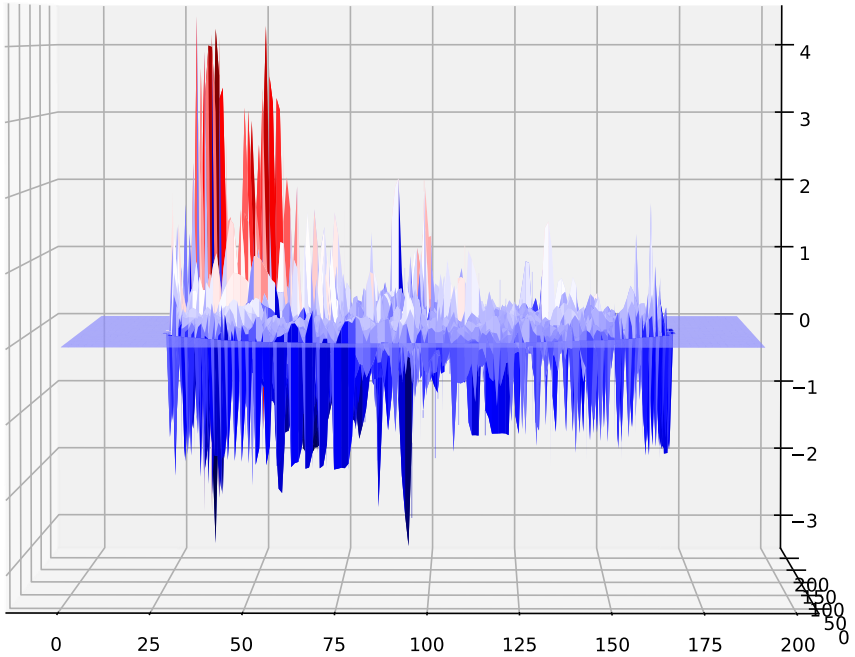


PC 2 PCA vs. difference image of two exams

Principal Component 2



Second - first MRI

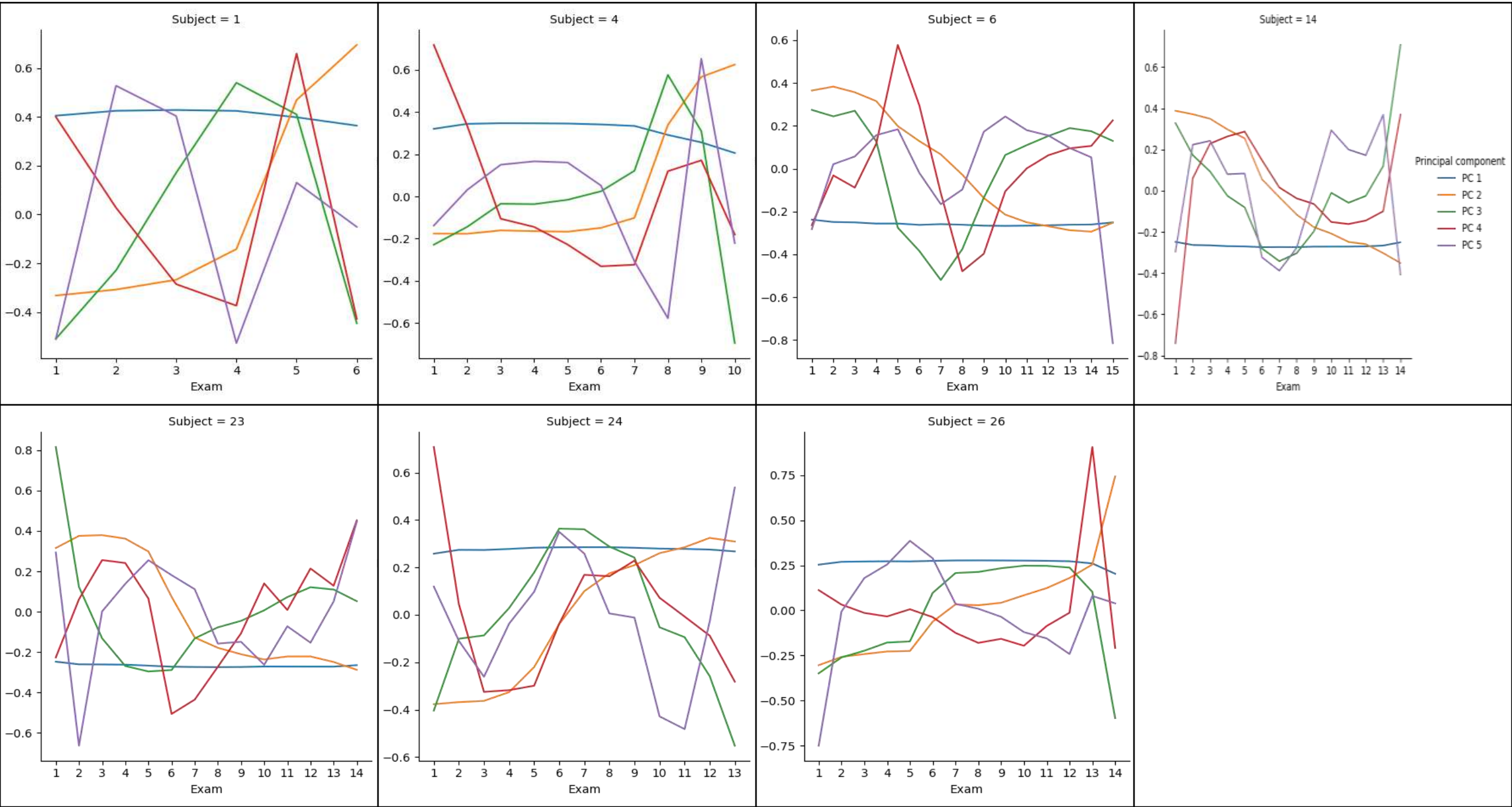


Subject (t1c)	Component describing ventricle change
1	2,3,4
4	2,3
6	2
14	2,3
23	2,3
24	2,3
26	2,3

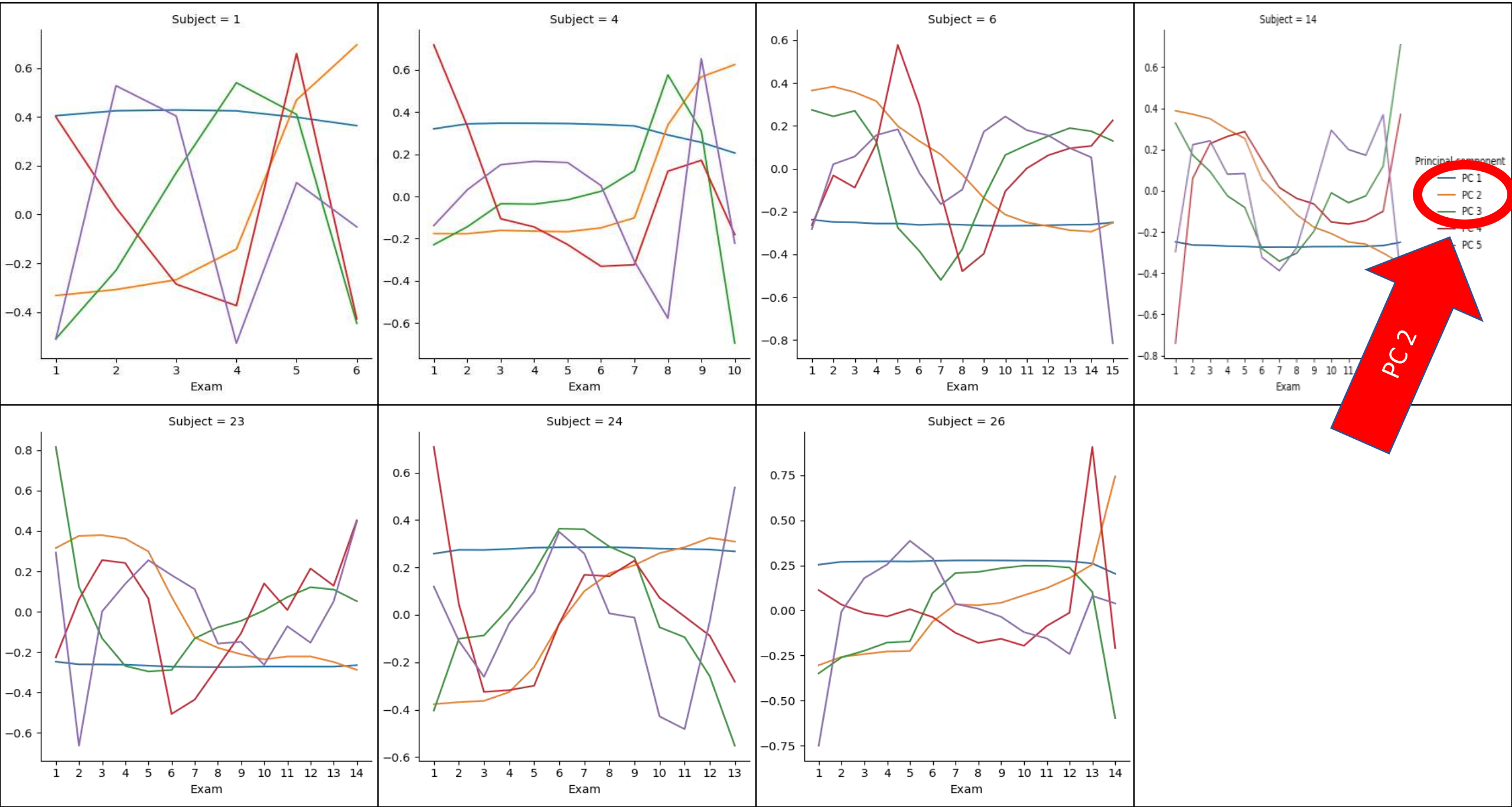
What is component 2?

- High intensity change caused by expanding ventricles

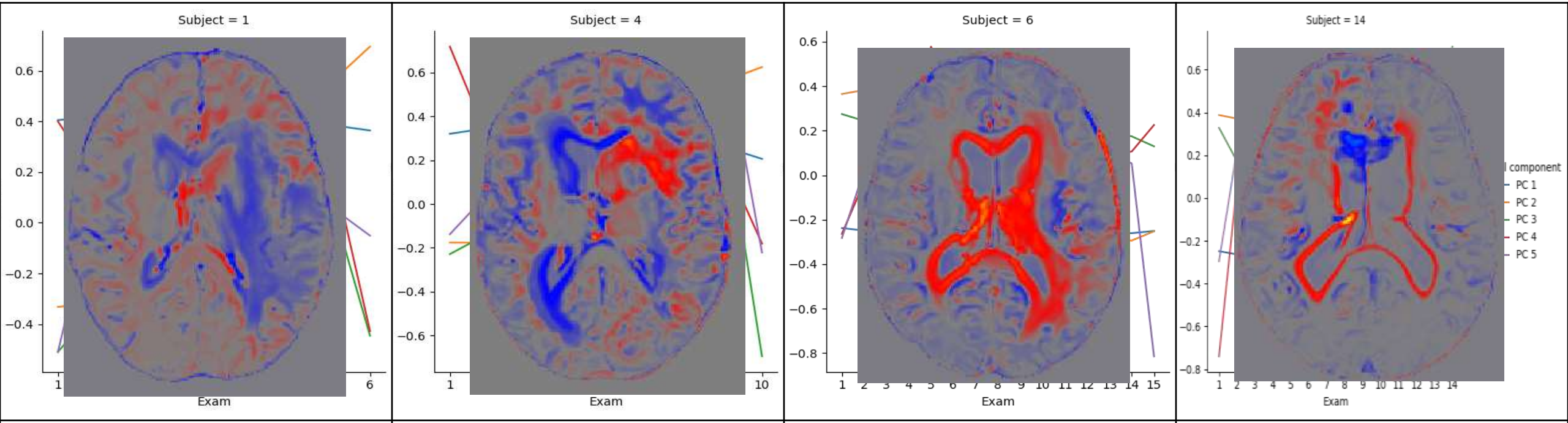
1 subject, 1 PCA, variable contribution (variable=exam)

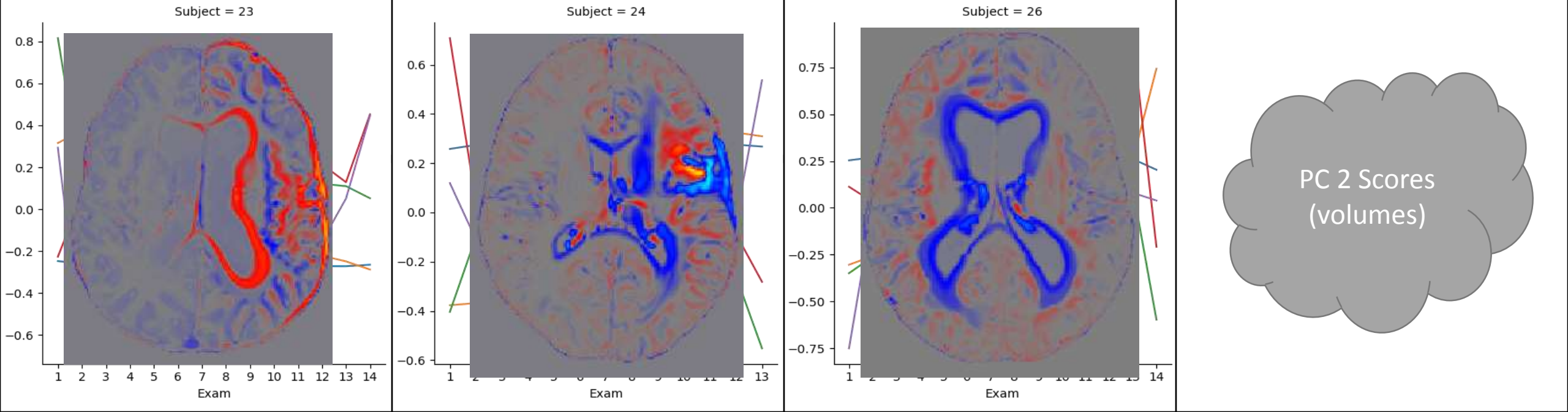


1 subject, 1 PCA, variable contribution (variable=exam)



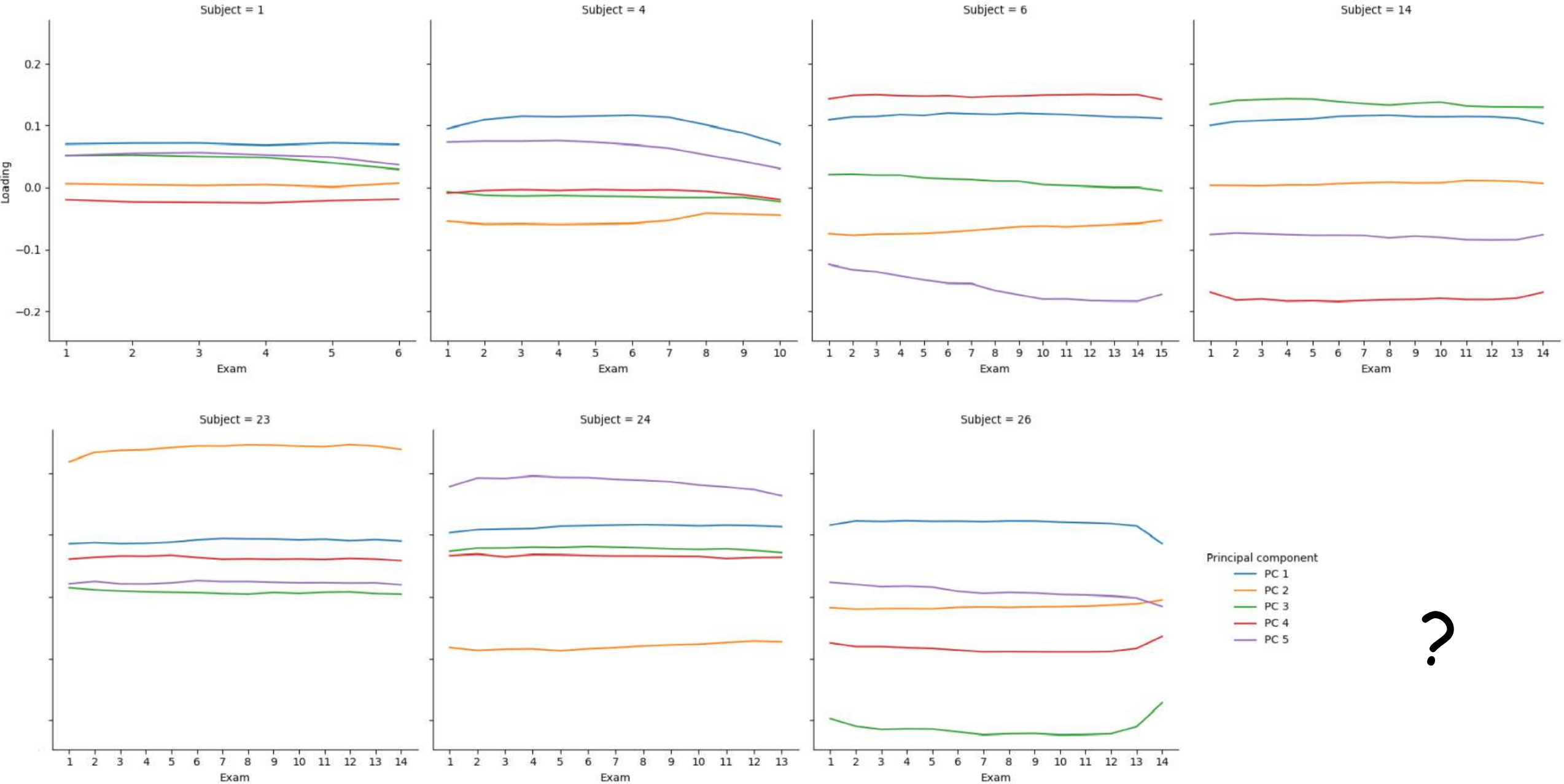
1 subject, 1 PCA, variable contribution (variable=exam)



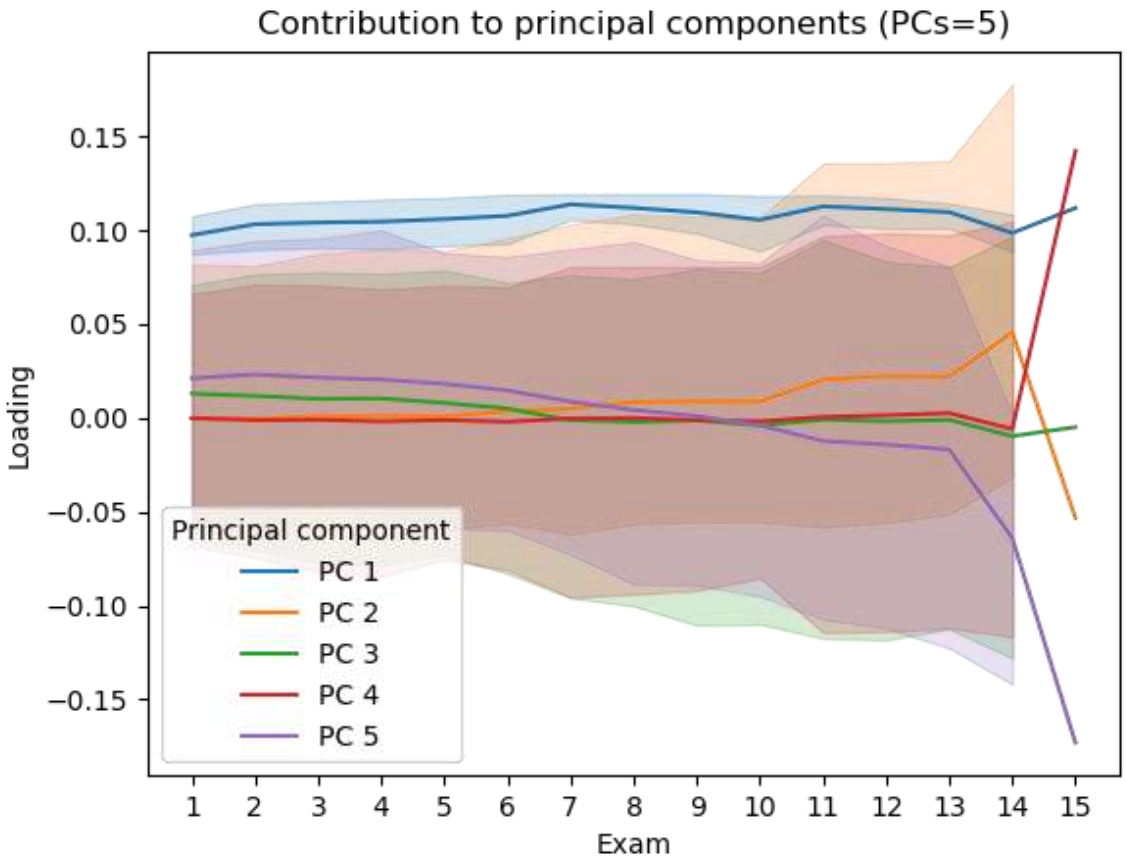


PC 2 Scores (volumes)

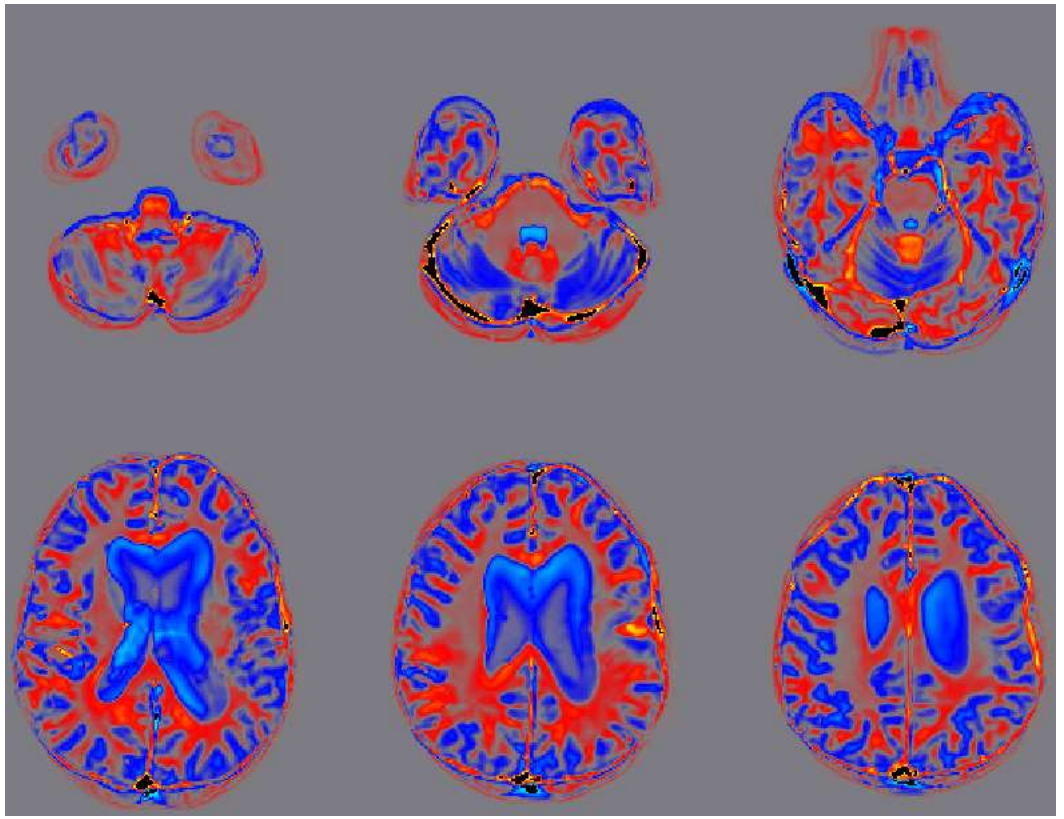
all subjects, 1 PCA, variable contribution (variable=exam)



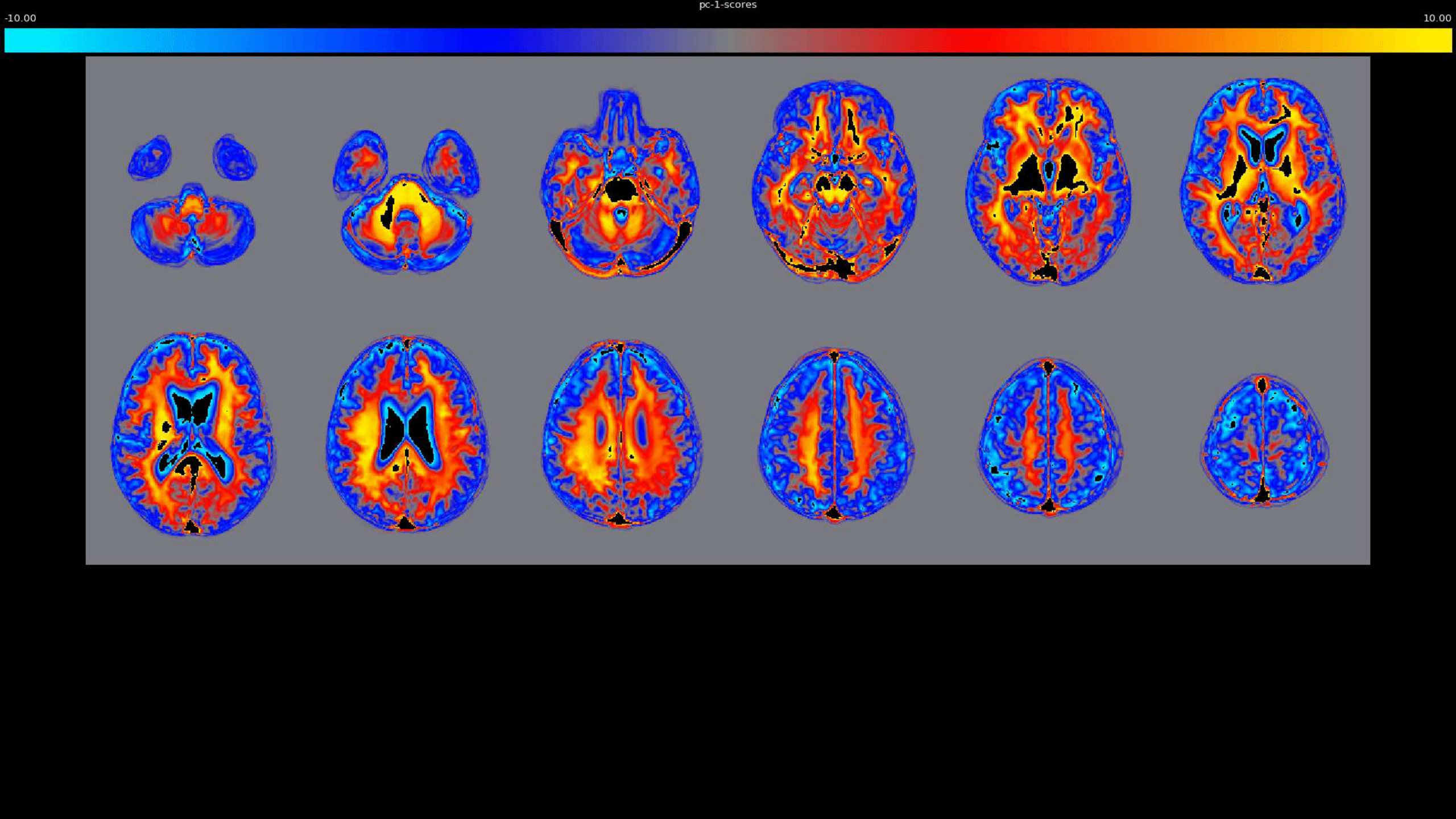
all subjects, 1 PCA, variable contribution



Loadings: Mean variable importance



Scores for PC 2


pc-1-scores
-10.00
10.00

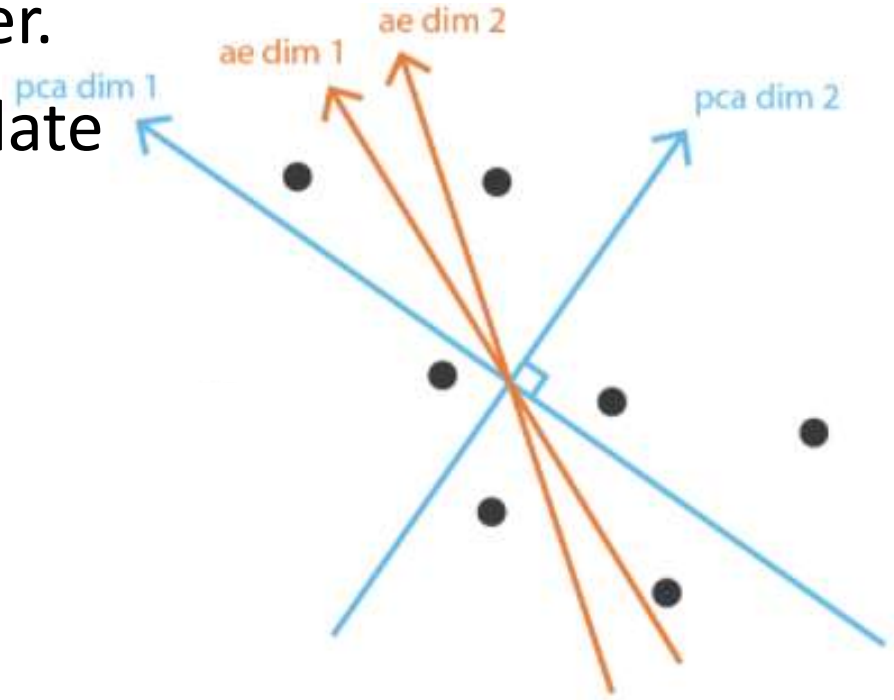
Summary PCA

- PCA on longitudinal MRI can describe ventricle change for a single subject (all exams, PC2). This supports hypothesis 1 (stable ventricle change)
- Stable ventricle volume increase can be quantified with PCA loadings and scores
- One PCA model of multiple subjects and exams fails to separate ventricle change into a distinct component

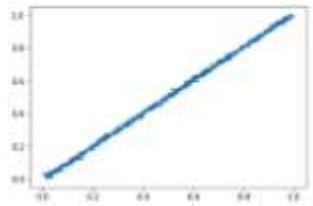
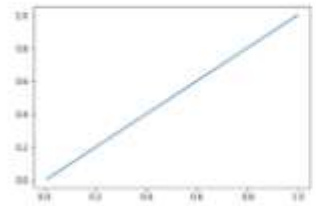
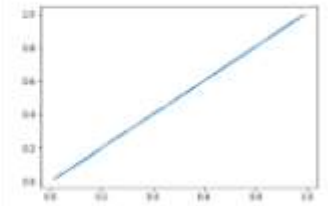
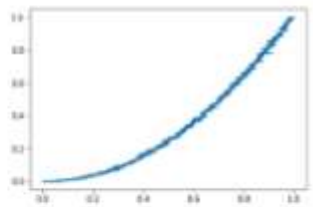
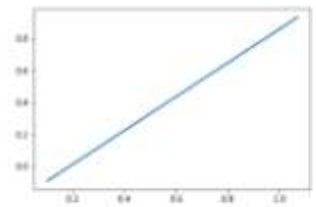
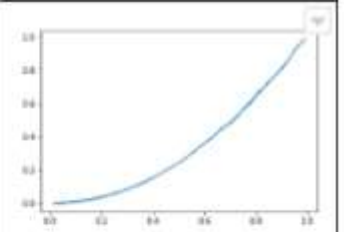
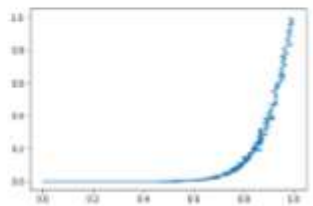
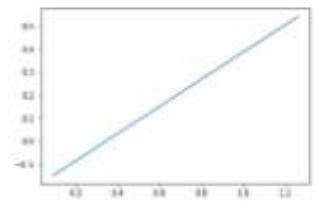
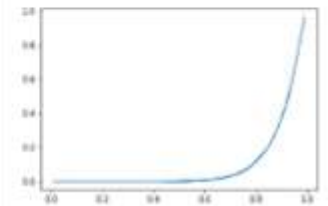
Autoencoder (AE)

- Dimensionality reduction as a computational graph problem
- Reduced dimensional representation of X is learnt by reconstructing inputs (rows) using encoder and decoder.
- Latent variables (dimensions) can correlate
- Possible to compute PCA loadings using AE weights[1]

$$X = \begin{bmatrix} x_{11} & \cdots & x_{1N} \\ \vdots & \ddots & \vdots \\ x_{M1} & \cdots & x_{MN} \end{bmatrix}$$



[1]https://arxiv.org/abs/1804.10253

Function	Feature Space	PCA Reconstruction	Auto Encoder Reconstruction
$y=mx+c$			
$y=mx^2+c$			
$y=mx^8+c$			

https://towardsdatascience.com/autoencoders-vs-pca-when-to-use-which-73de063f5d7

PCA-AE correspondence requirements[1]

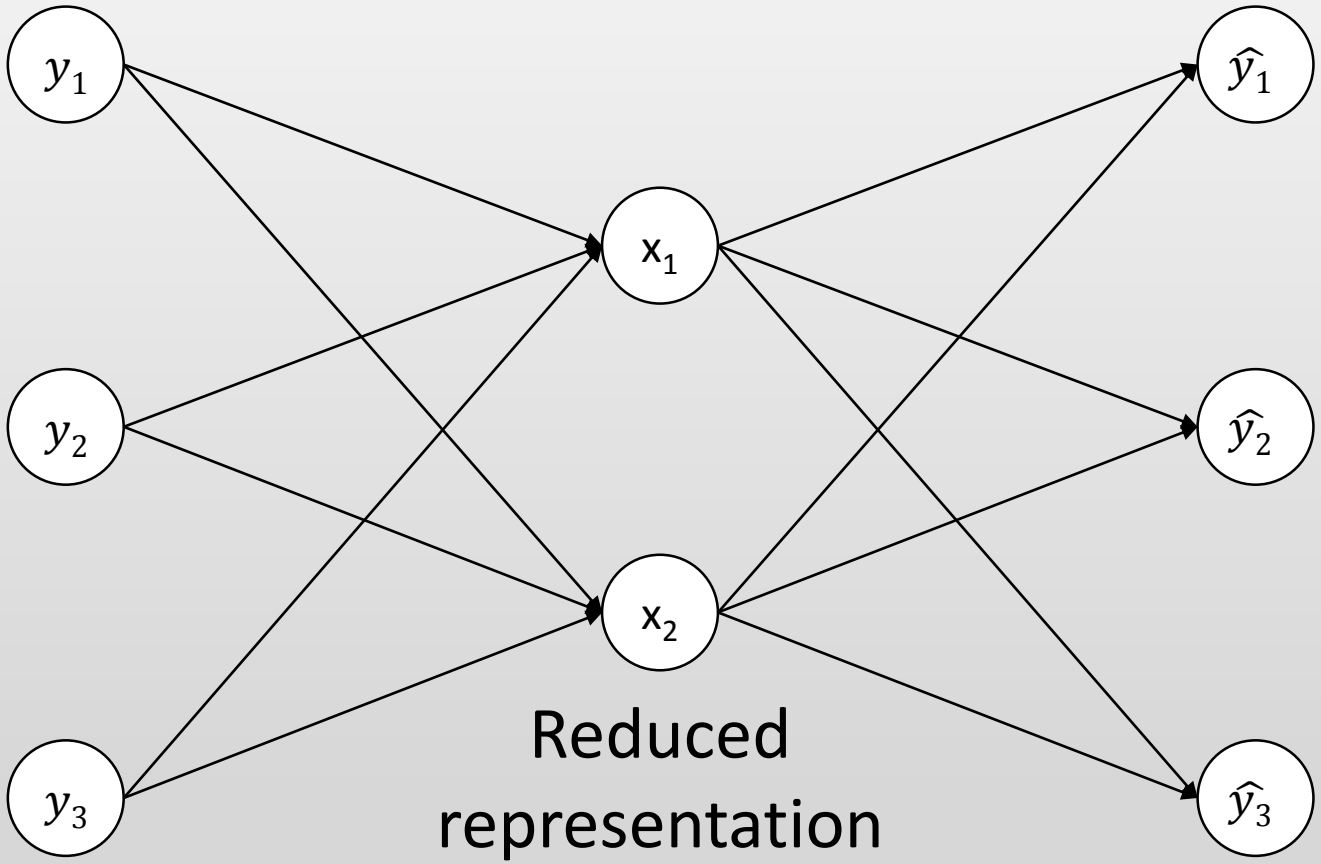
- Three-layer fully connected network: encoder, number of components, decoder
- No activation functions (=linear; f(x) = x)
- Mean squared error loss function
- L_2 weight regularization (layer-wise)

[1]https://arxiv.org/abs/1804.10253

Autoencoder

True (Y)

Reconstructed $(\hat{Y})$

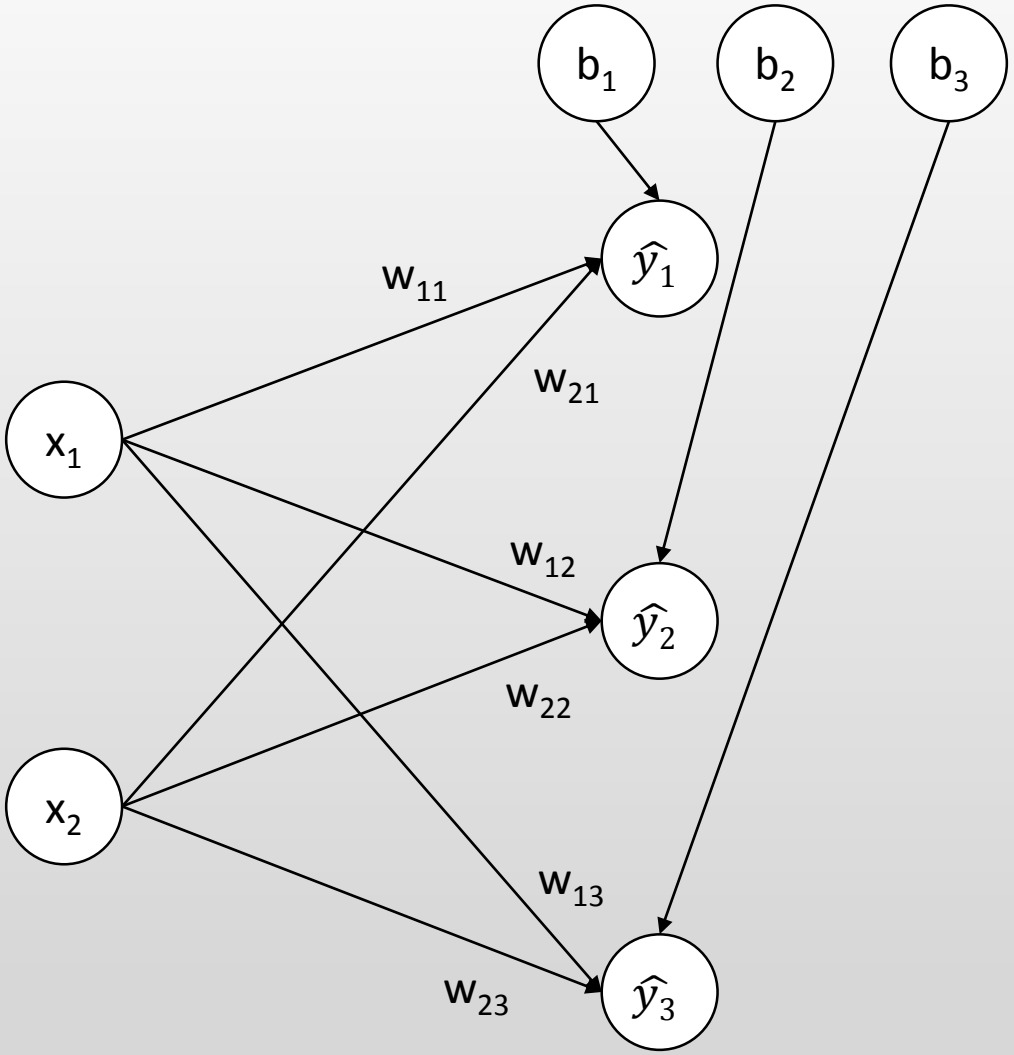


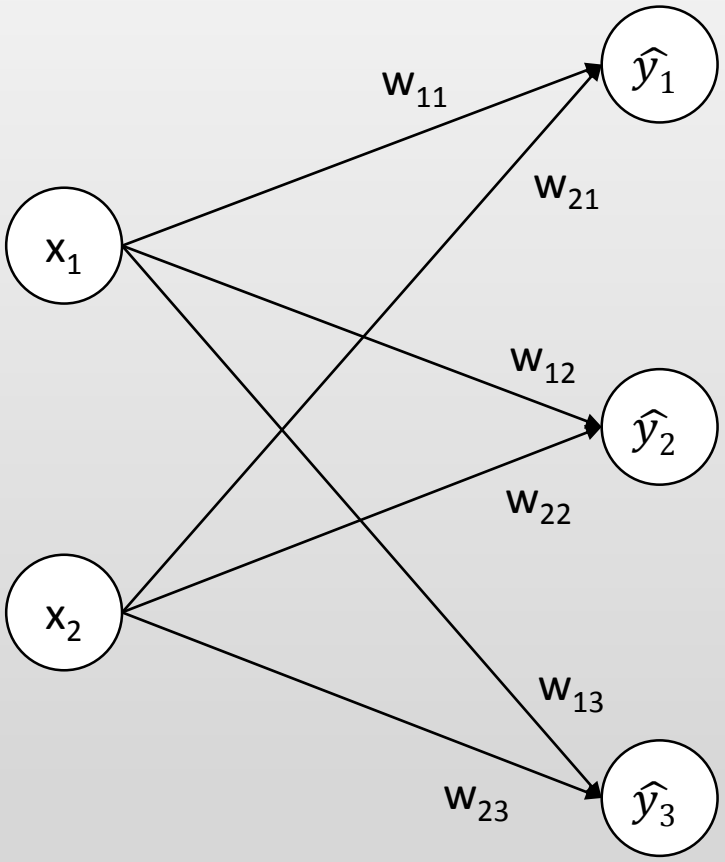
Reduced representation

Encoder

Decoder

The mean squared error loss function


b1
b2
b3
ŷ1
ŷ2
ŷ3
x1
x2
w11
w21
w12
w22
w13
w23



$$\hat{y}_1 = w_{11}x_1 + w_{21}x_2$$
$$\hat{y}_2 = w_{12}x_1 + w_{22}x_2$$
$$\hat{y}_3 = w_{13}x_1 + w_{23}x_2$$

$$\hat{y} = \begin{bmatrix} \hat{y}_1 \\ \hat{y}_2 \\ \hat{y}_3 \end{bmatrix} \qquad W = \begin{bmatrix} w_{11} & w_{21} \\ w_{12} & w_{22} \\ w_{13} & w_{33} \end{bmatrix} \qquad x = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$

$$\hat{y} = Wx$$

$$ForwardLoss := \|\hat{y} - y\|_2^2 = \frac{1}{3}\sum_{i=1}^{3}(\hat{y}_i - y_i)^2$$

$$MSELoss := \frac{1}{N}\sum_{j=1}^{N} ForwardLoss(j)$$

N: Batch size

The weight regularization

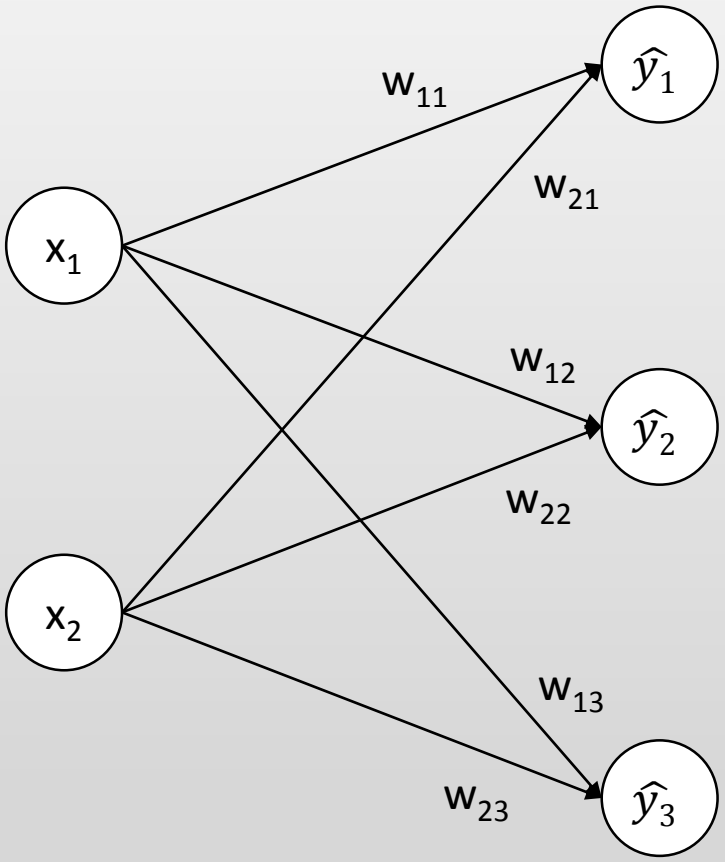
$$WeightRegularizedMSELoss := MSELoss + \alpha \sum_{i=1}^{3} \sum_{j=1}^{2} |wij|2$$

α: penalty term, f. ex. 0.01

- Encourages the network to keep the weights small
- Technique to reduce overfitting of the training dataset
- Applied on a per-layer basis
- Penalizing a network based on the size of the weighs during training

Decoder

$$\hat{y}_1 = w_{11}x_1 + w_{21}x_2$$
$$\hat{y}_2 = w_{12}x_1 + w_{22}x_2$$
$$\hat{y}_3 = w_{13}x_1 + w_{23}x_2$$



$$\hat{y} = \begin{bmatrix} \hat{y}_1 \\ \hat{y}_2 \\ \hat{y}_3 \end{bmatrix} \qquad W = \begin{bmatrix} w_{11} & w_{21} \\ w_{12} & w_{22} \\ w_{13} & w_{33} \end{bmatrix} \qquad x = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$

$$\hat{y} = Wx$$

$$ForwardLoss := \|\hat{y} - y\|_2^2 = \frac{1}{3}\sum_{i=1}^{3}(\hat{y}_i - y_i)^2$$

$$WeightRegularizedMSELoss := \frac{1}{N}\sum_{i=1}^{N} ForwardLoss(i) + \alpha \sum_{i=1}^{3} \sum_{j=1}^{2} |wij|2$$

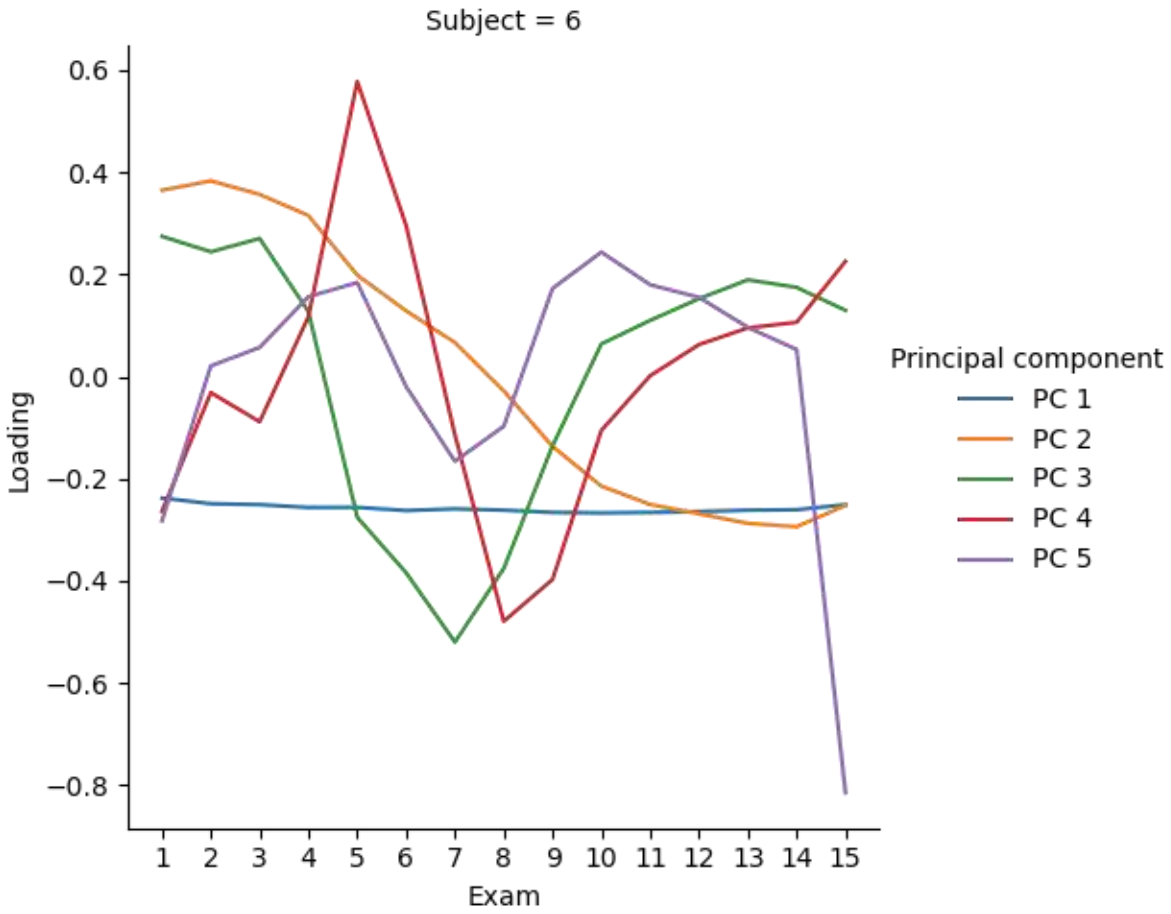
N: Batch size

Experimental setup (similar to[1])

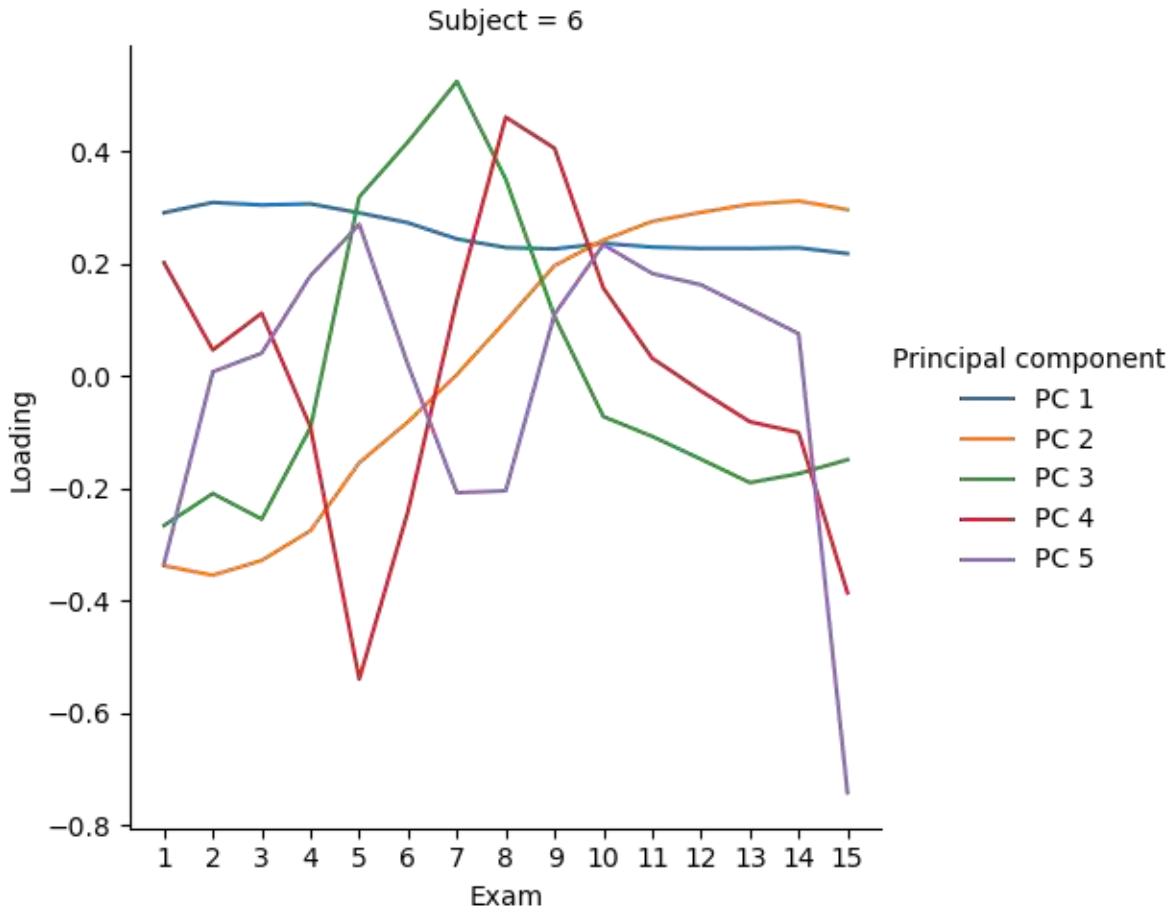
- Learning rate: 10^{-4}
- Weight regularization (α): $5*10^{-4}$
- Weight update rule: Adam
- Batch-size: 4
- (row) shuffle (!)
- Epochs: 1

[1]https://arxiv.org/abs/1804.10253

PCA and AE model of subject 6 (all exams) – Variable Importance

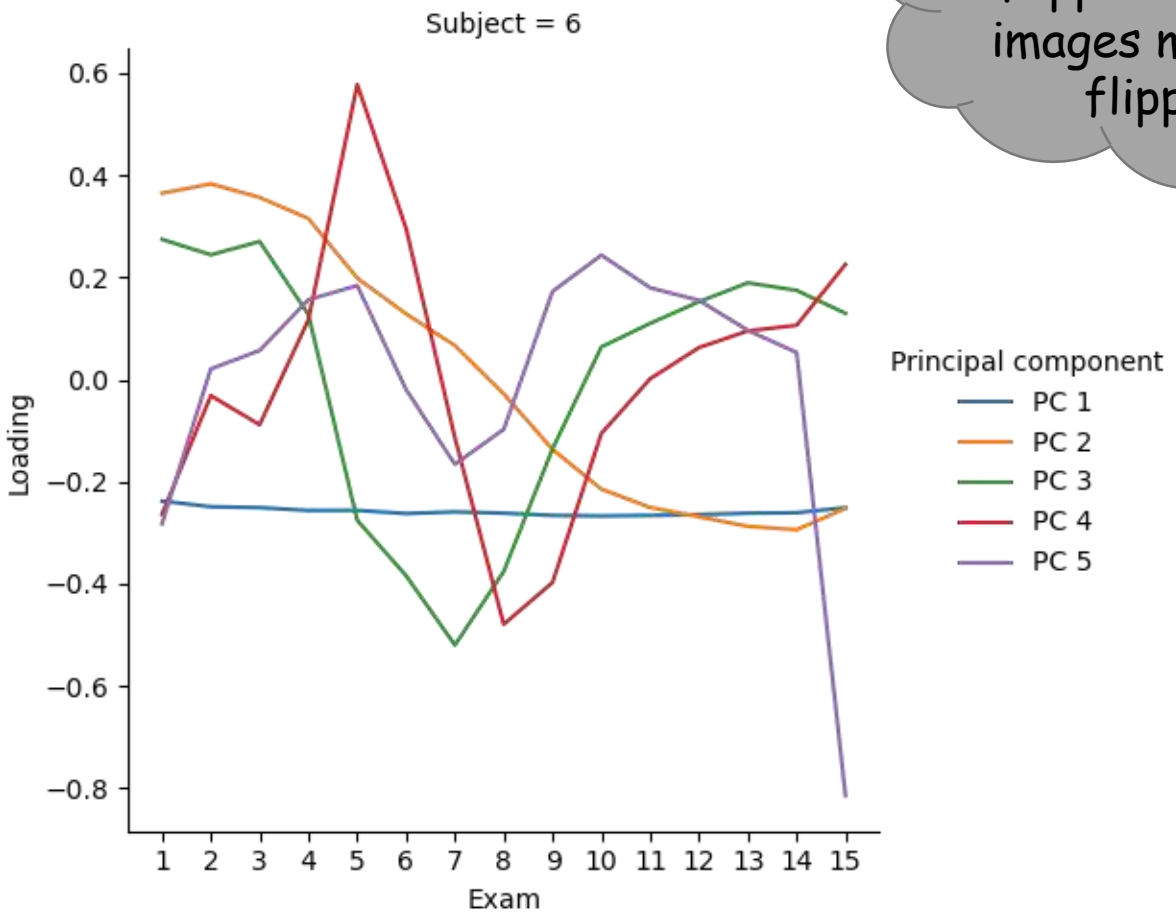


PCA loadings from SVD on X

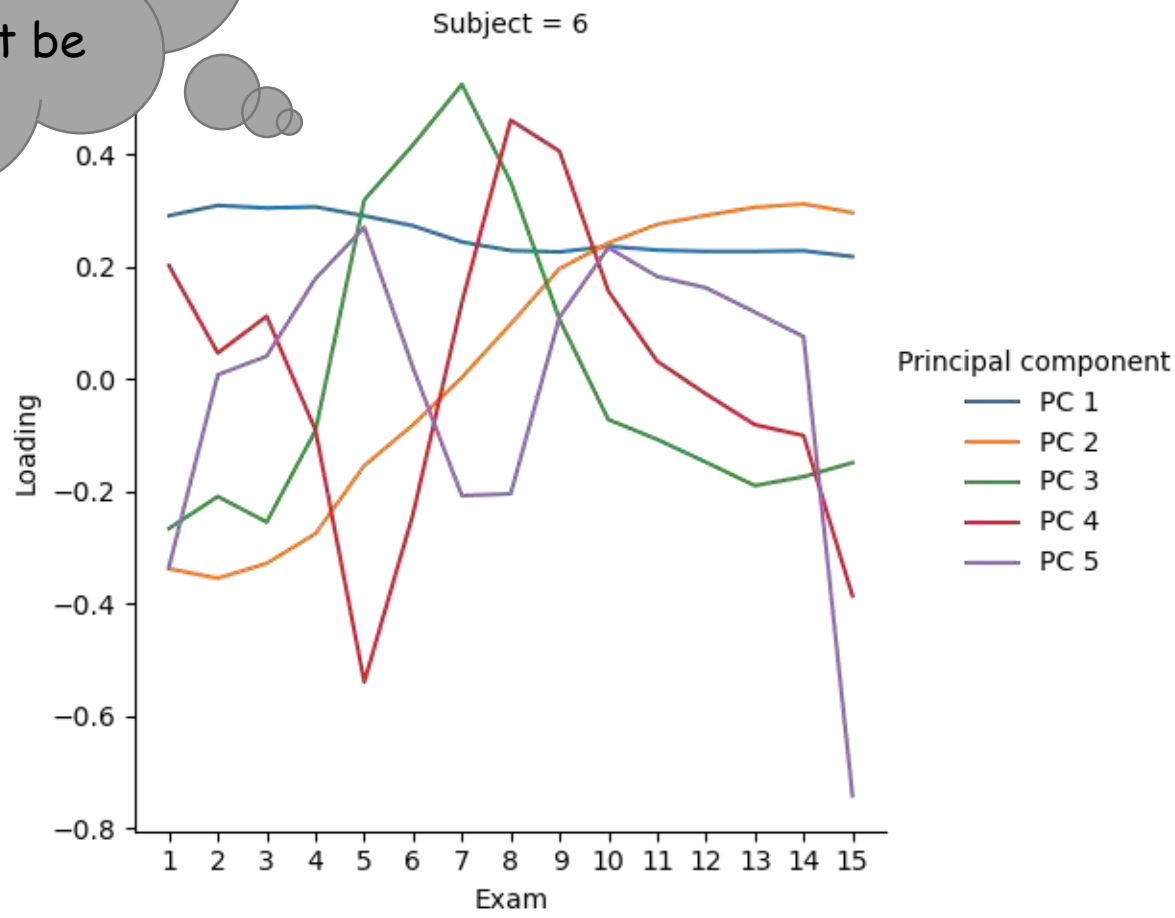


PCA loadings from SVD on AE weights (decoder), trained on X

Variable contributions for PC 1-4 are flipped – score images must be flipped



PCA loadings from SVD on X



PCA loadings from SVD on AE weights (decoder), trained on X

Summary AE

- AE can present contributions of separate input variables to (principal) components, like loadings in PCA
- Interpretability method
- Starting point to test more advanced networks for learning interpretable representations of disease (convolutional, transformers, attention, etc.)

Conclusion and beyond

- Theoretical: Connection between the linear independent (orthogonal) features from PCA, and linear dependent features of AE, using SVD of decoder weights of the AE
- Practical: Possible to compute variable importance for large datasets with a simple autoencoder as if it were PCA
- Clinical: Ventricle change with time can be quantified using PCA and AE. PCA and AE indicate that ventricle change is the most stable temporal pattern with disease. This is an example and introduction to large scale analysis of MRI for categorizing disease. Potential outcomes are predictions for a new subject based on existing data, such as predicting treatment response and overall survival
- Combining multivariate methods with “AI” models and frameworks is a good starting point for building up intuition for interpreting more advanced neural network models, which is important in medicine