



Developing Human
Connectome Project

dHCP data tutorial

Dr Emma C. Robinson Dr Maria Deprez
@emrobSci

Group Meetings 21/05/2019

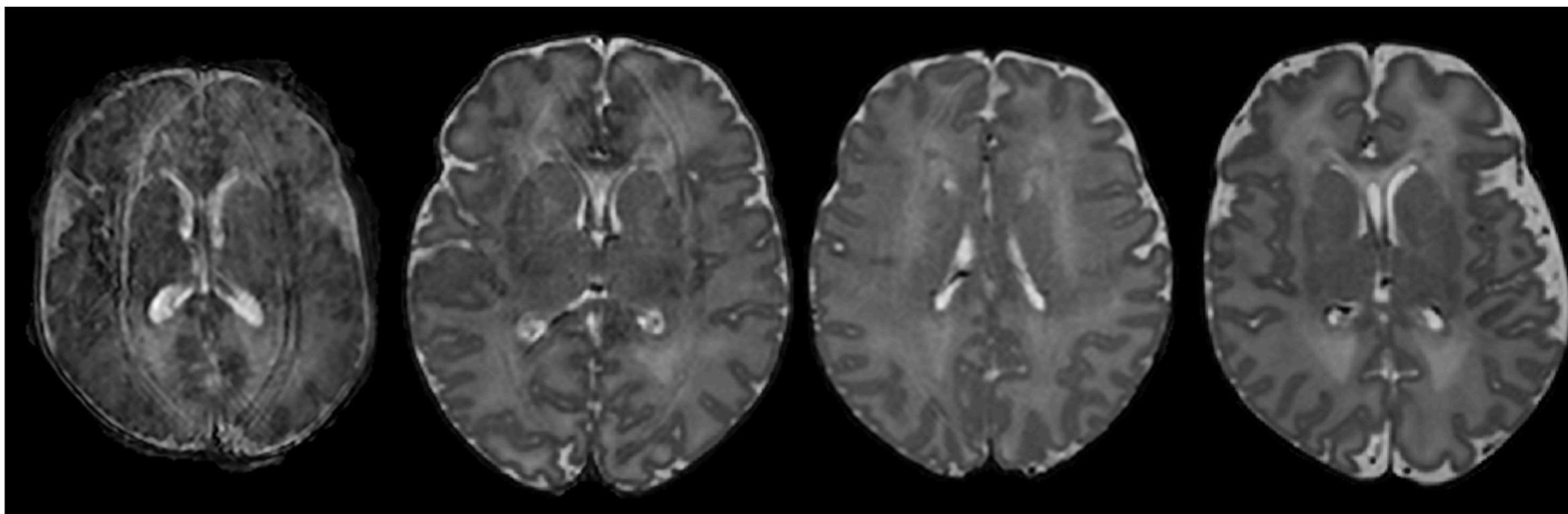
Challenges of working with developing data

Challenges of working with developing data

- Developing data is affected by

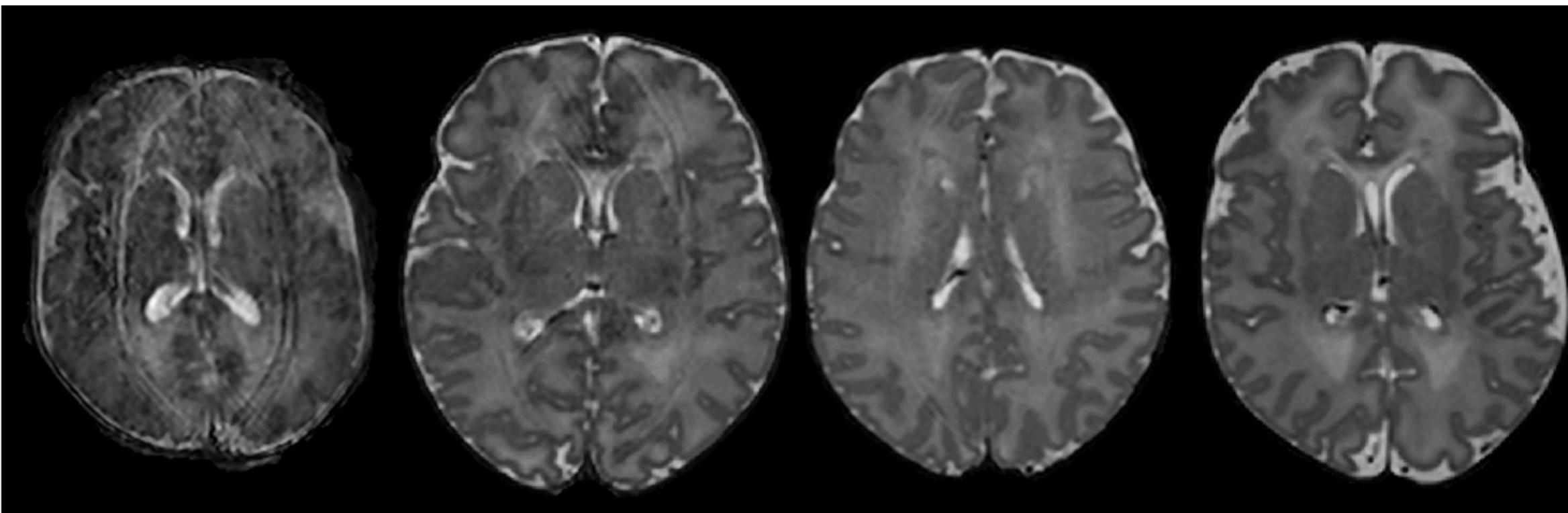
Challenges of working with developing data

- Developing data is affected by
 - ▶ Motion (severe cases account for < 2%)



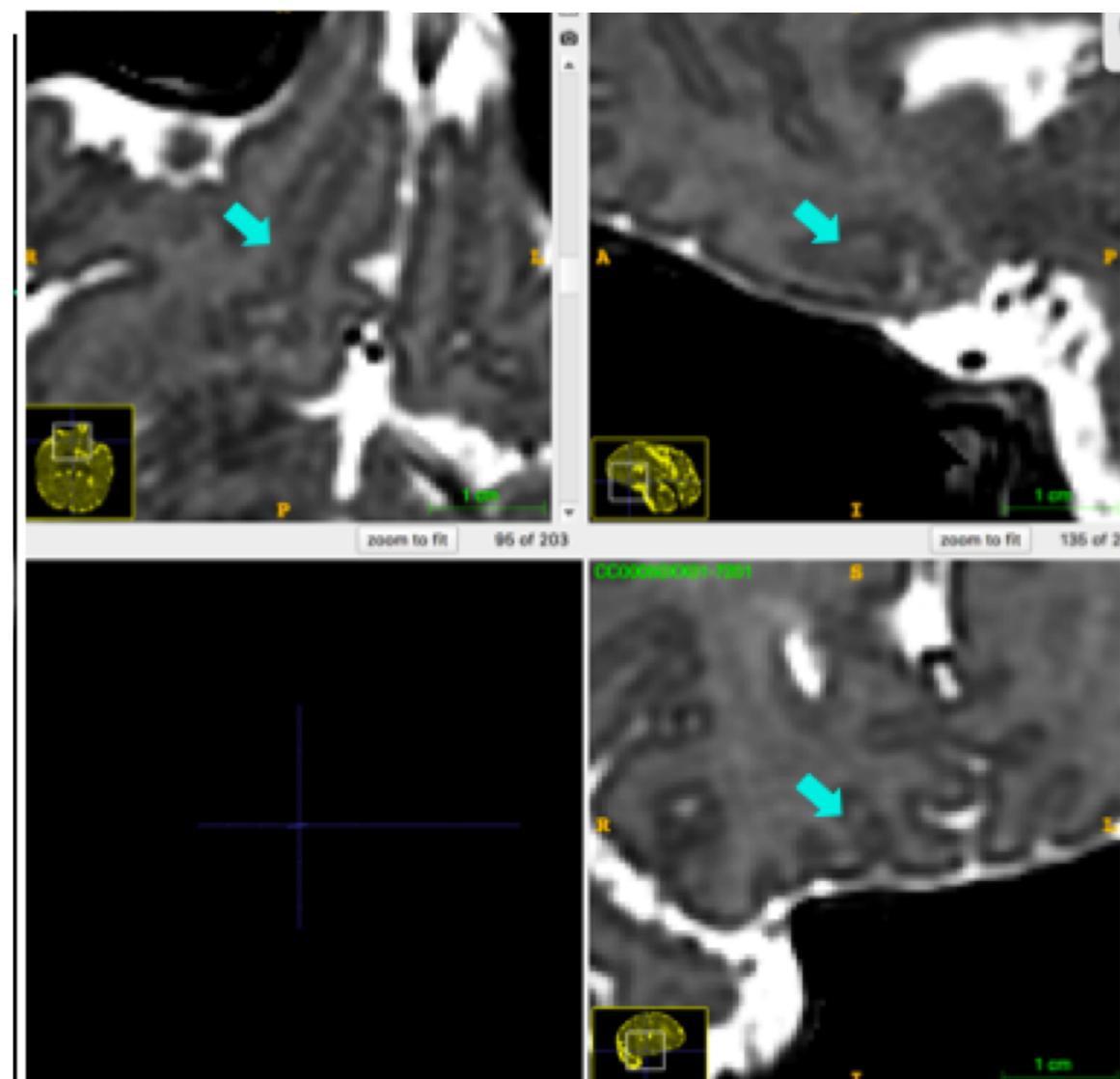
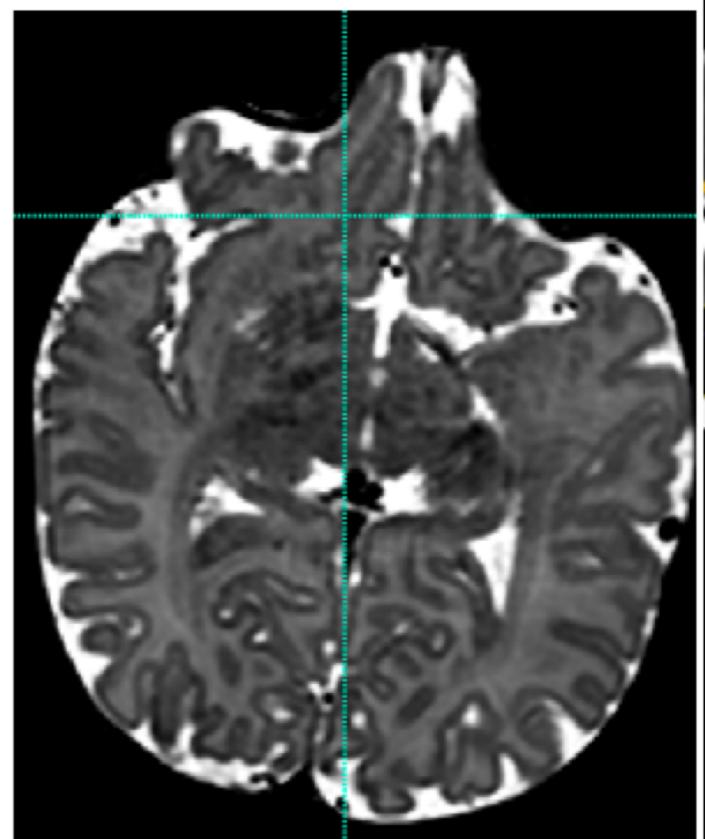
Challenges of working with developing data

- Developing data is affected by
 - ▶ Motion (severe cases account for < 2%)
 - ▶ Limited scan times



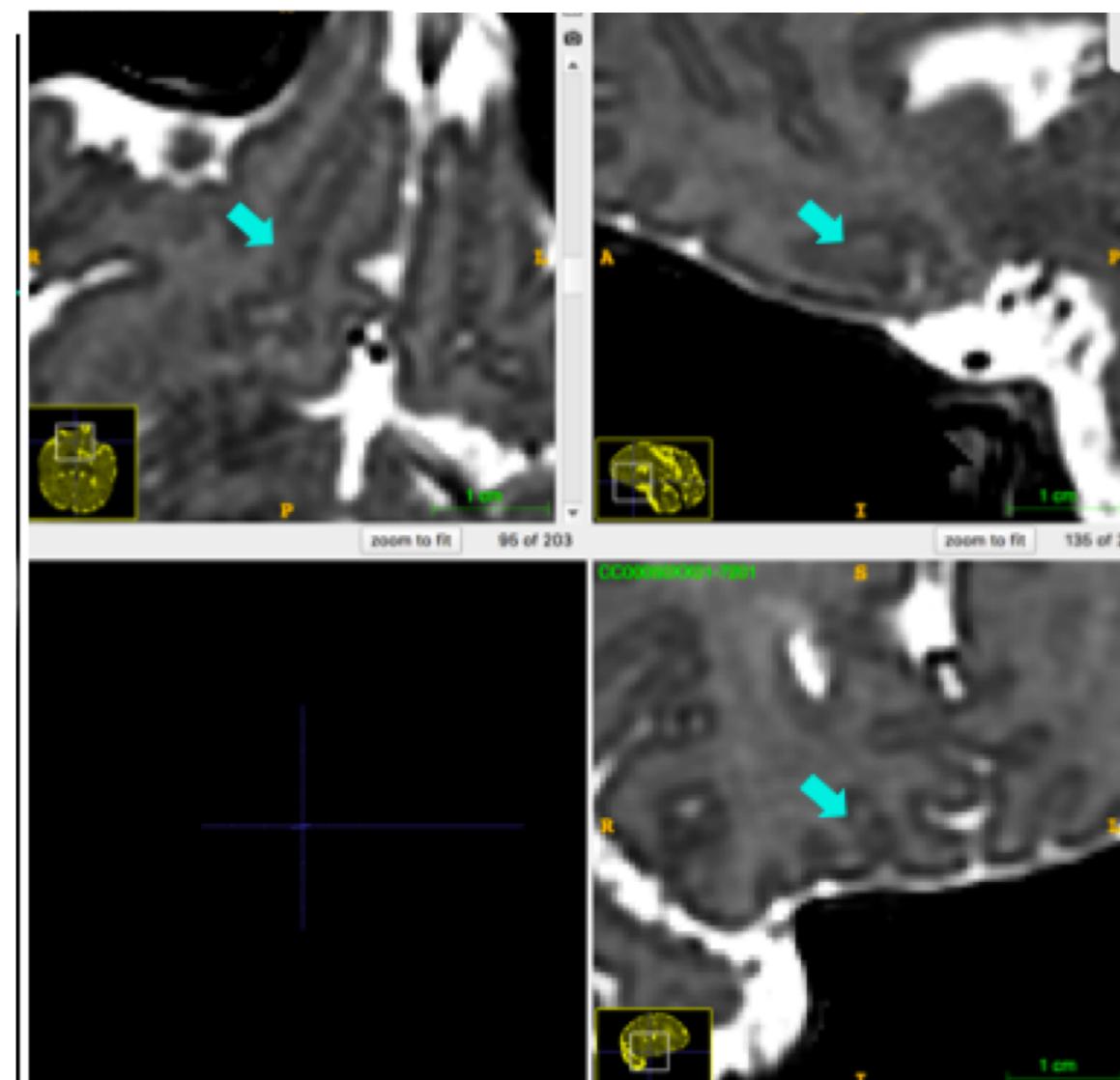
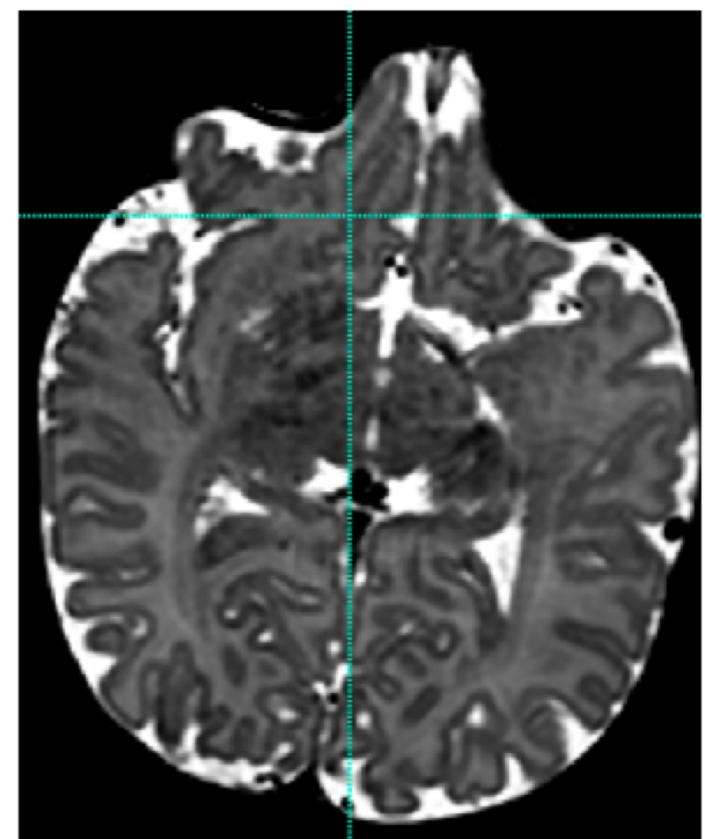
Challenges of working with developing data

- Developing data is affected by
 - ▶ Motion (severe cases account for < 2%)
 - ▶ Limited scan times
 - ▶ Relatively low resolution



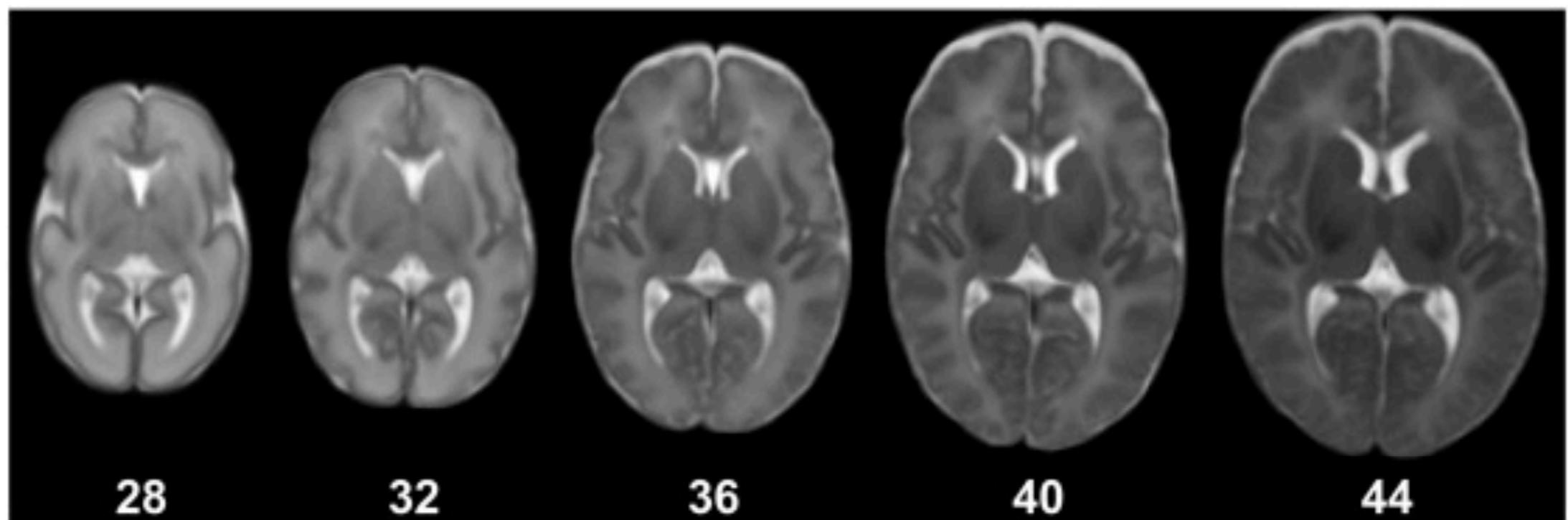
Challenges of working with developing data

- Developing data is affected by
 - ▶ Motion (severe cases account for < 2%)
 - ▶ Limited scan times
 - ▶ Relatively low resolution
 - ▶ Inverted contrast



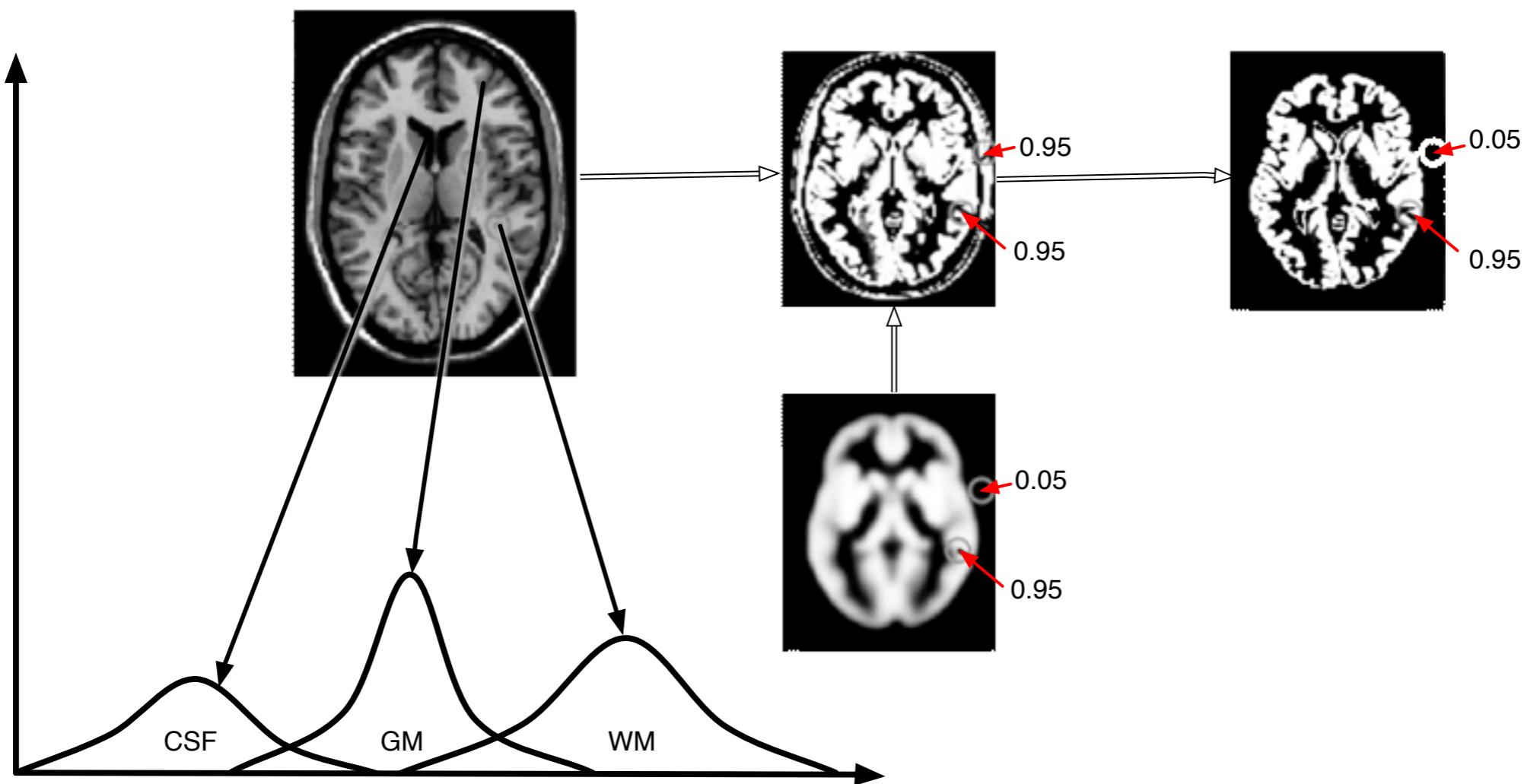
Challenges of working with developing data

- Developing data is affected by
 - ▶ Motion (severe cases account for < 2%)
 - ▶ Limited scan times
 - ▶ Relatively low resolution
 - ▶ Inverted contrast
 - ▶ spatio-temporal evolution



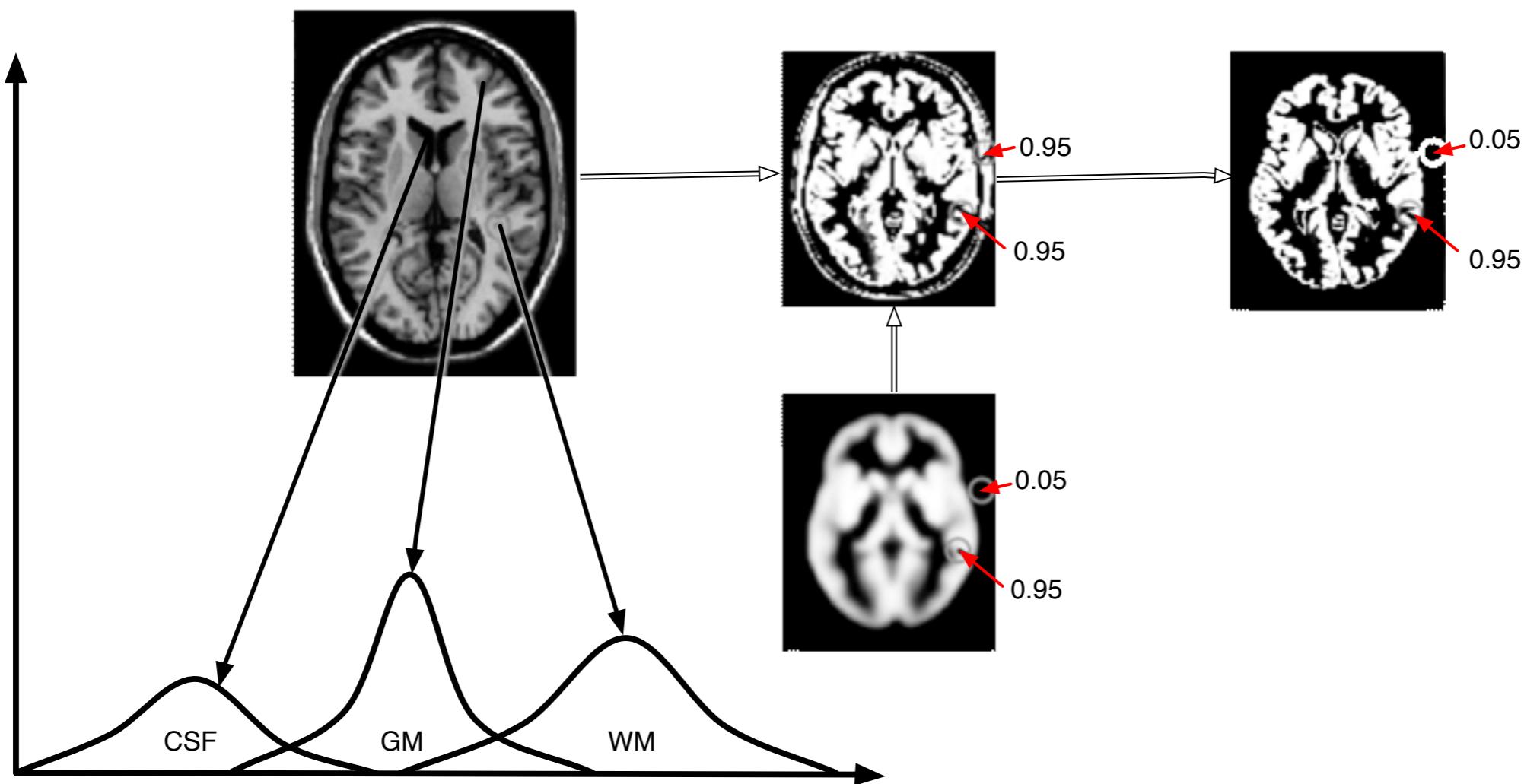
Tissue segmentation

- Widely used in medical image segmentation, e.g.
 - Wells et al. 1996, van Leemput et al. 1999



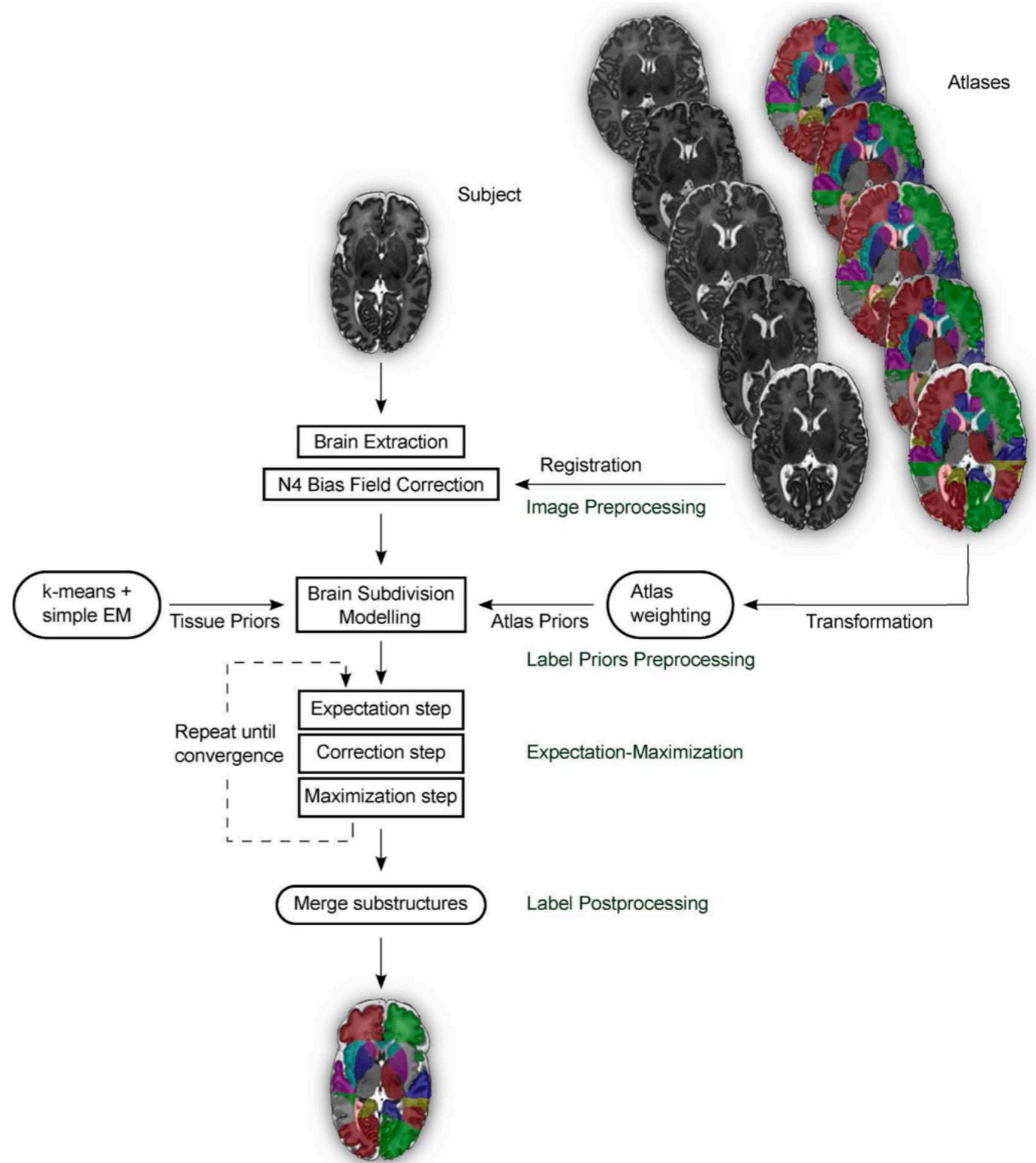
Tissue segmentation

- Widely used in medical image segmentation, e.g.
 - Wells et al. 1996, van Leemput et al. 1999
- Find the label settings that maximise the data likelihood function.



Neonatal Tissue Segmentation:

- Expectation maximisation
 - Maximising likelihood of mixture of Gaussians
- Prior from probabilistic template
- Smoothness imposed as a MRF (neighbouring points encouraged to have same labels)



dHCP Structural Pipeline

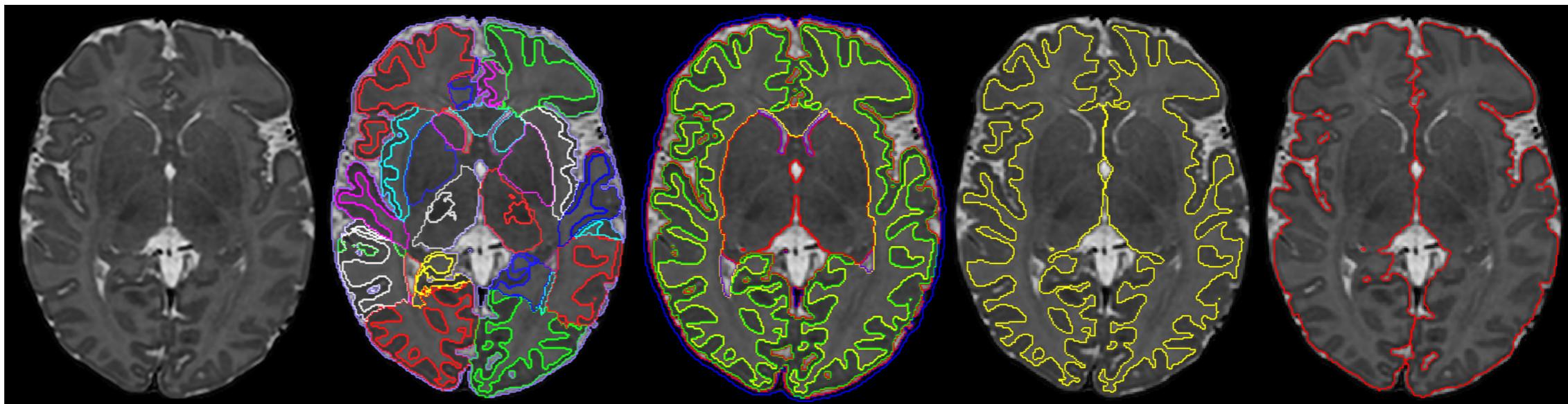
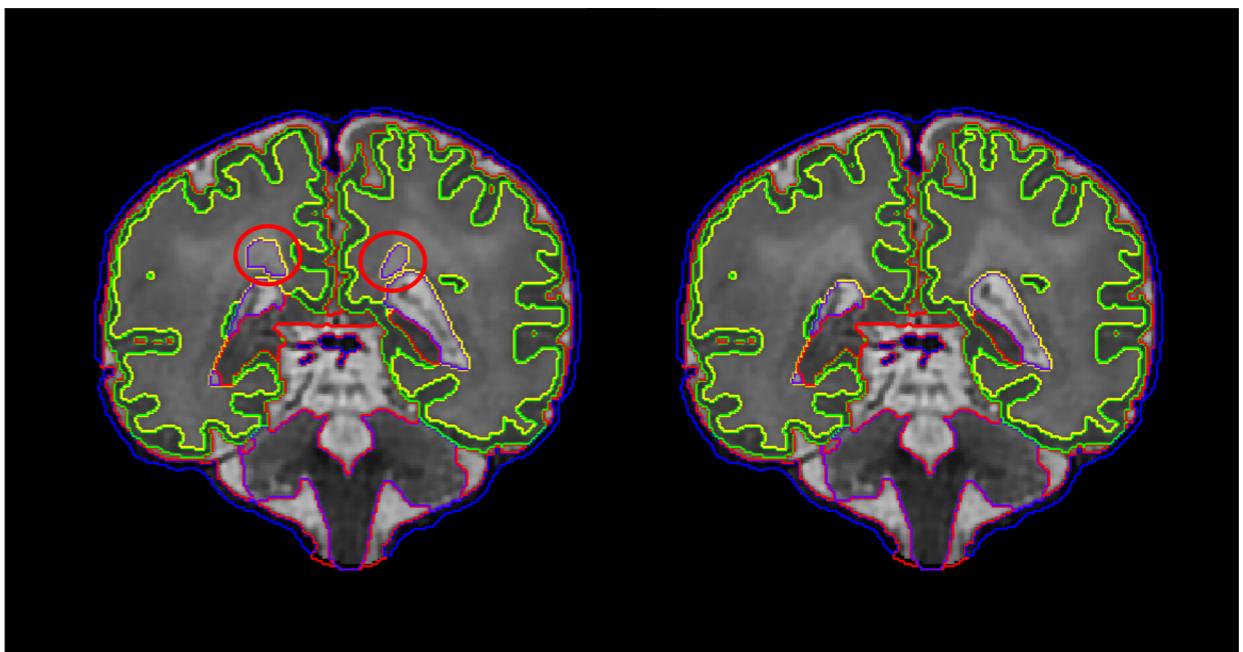
- Reconstruction with motion correction

dHCP Structural Pipeline

- Reconstruction with motion correction
- Refined Tissue segmentation
 - New tissue classes for e.g. hypo intense white matter (around ventricles)

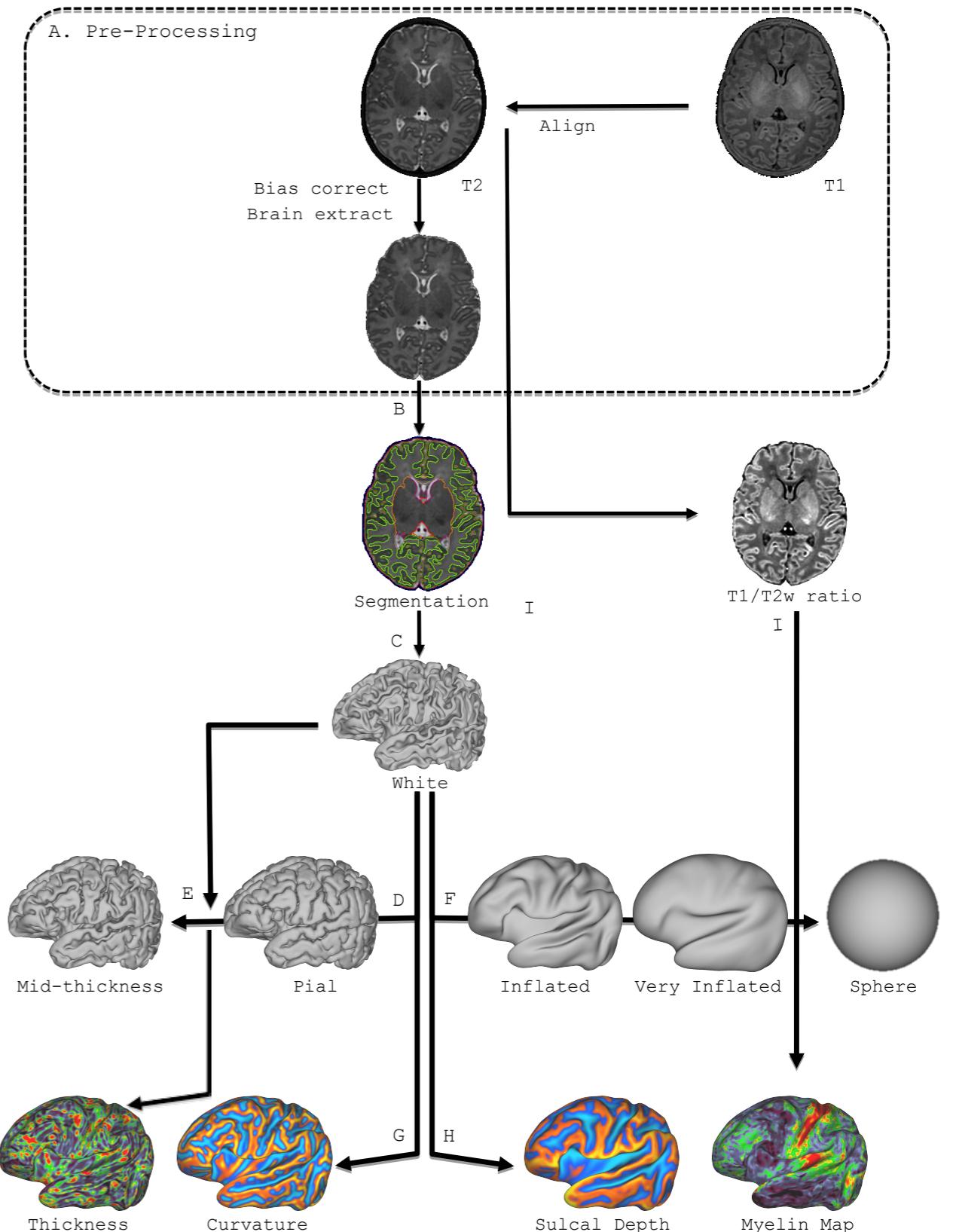
Makropoulos, Antonios, et al. "Automatic whole brain MRI segmentation of the developing neonatal brain." *IEEE transactions on medical imaging* 33.9 (2014): 1818-1831.

High intensity white matter correction



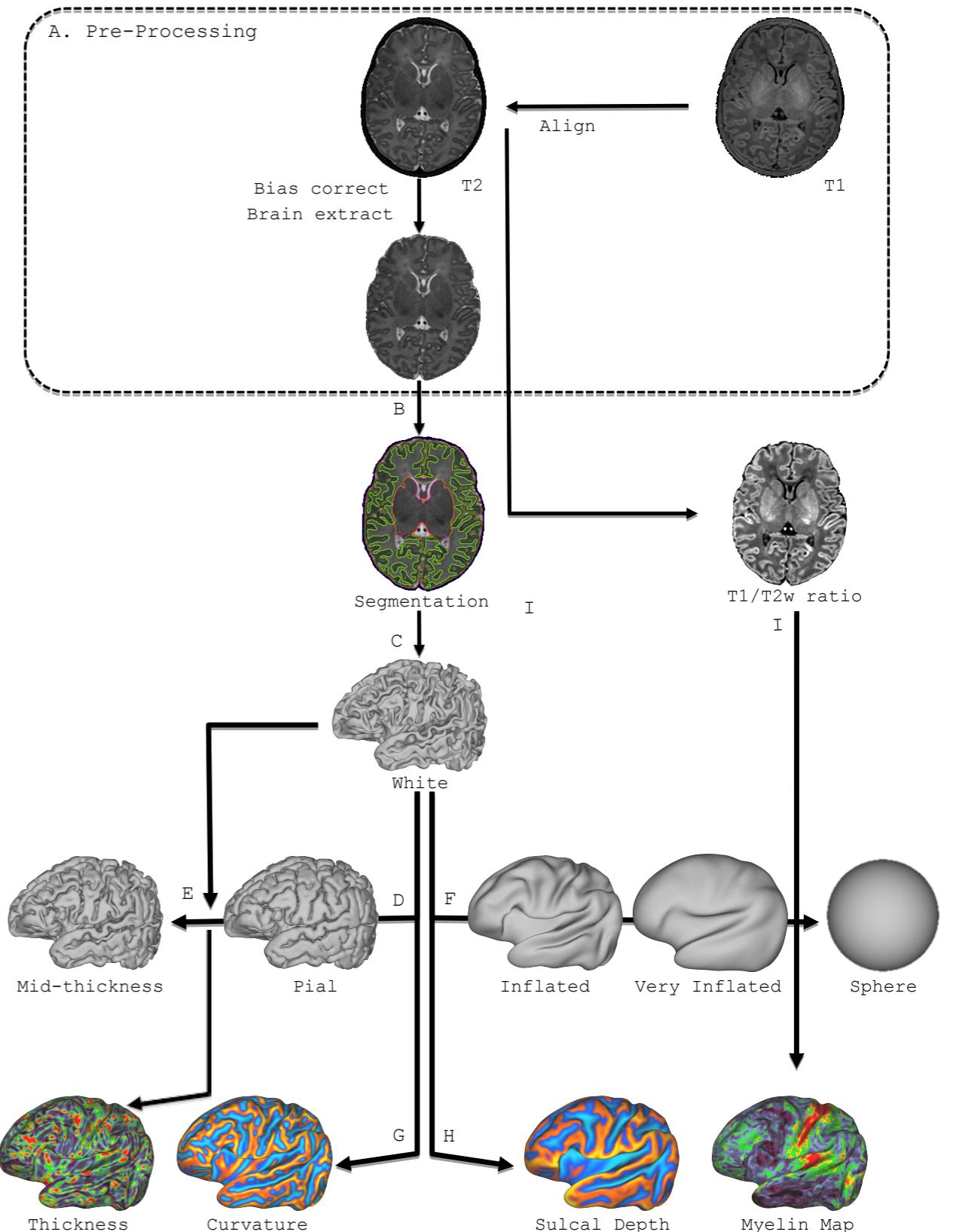
dHCP Structural Pipeline

- Reconstruction with motion correction
- Refined Tissue segmentation
 - New tissue classes for e.g. hypo intense white matter (around ventricles)



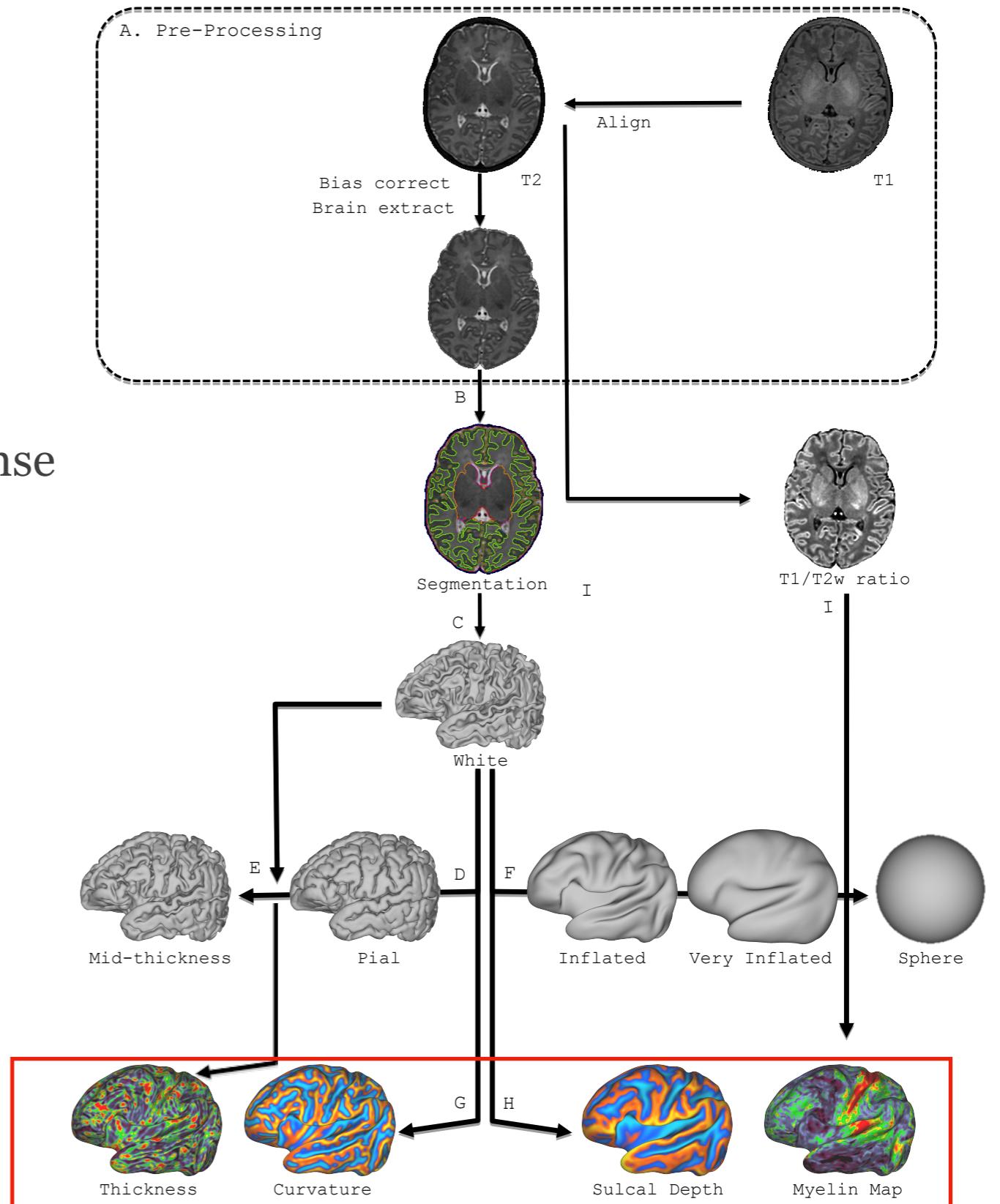
dHCP Structural Pipeline

- Reconstruction with motion correction
- Refined Tissue segmentation
 - New tissue classes for e.g. hypo intense white matter (around ventricles)
- Surface mesh modelling



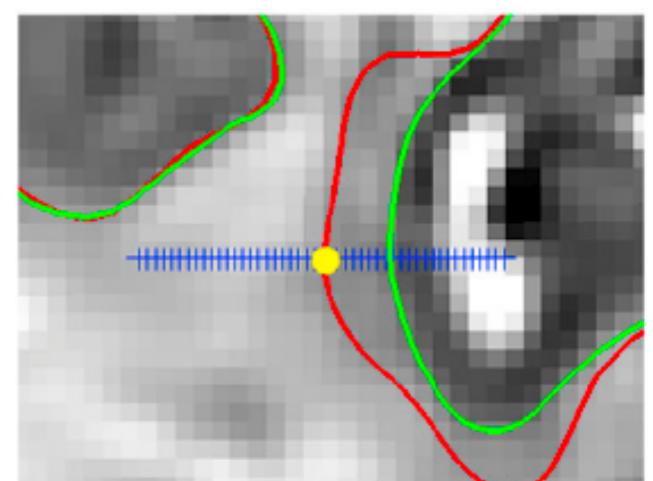
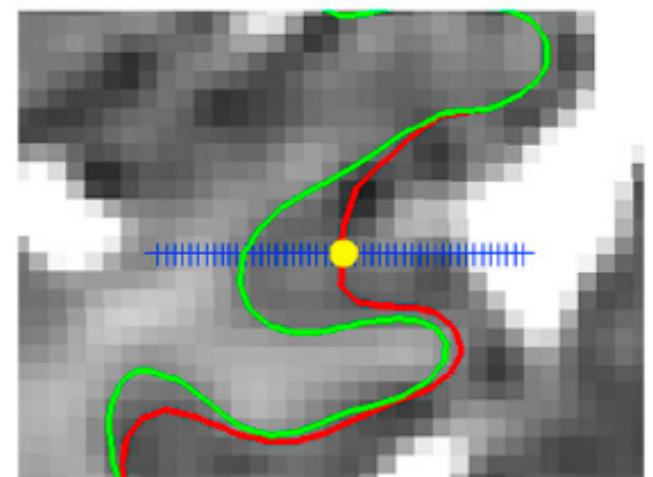
dHCP Structural Pipeline

- Reconstruction with motion correction
- Refined Tissue segmentation
 - New tissue classes for e.g. hypo intense white matter (around ventricles)
- Surface mesh modelling
- Feature Extraction



Surface mesh extraction

- White matter (WM) mesh extraction performed by fitting a closed genus-0 triangulated mesh to WM tissue segmentation
- Partial volume causes segmentation errors:
 - WM holes (WM misclassified as CSF)
 - undetected sulci (CSF misclassified as WM)
- Corrected using intensity based refinement
- Pial surface is then obtained by deforming the white-matter mesh towards the cGM/CSF boundary



Surface mesh extraction

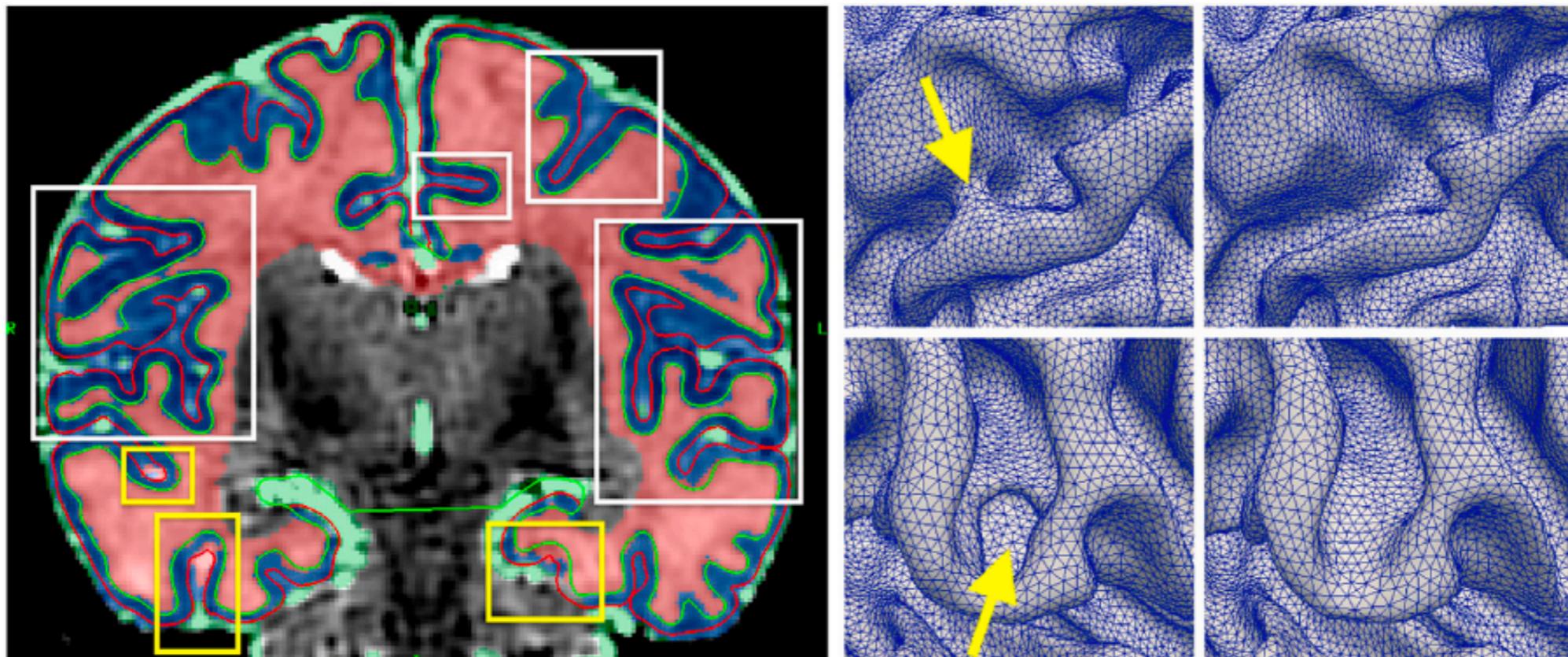


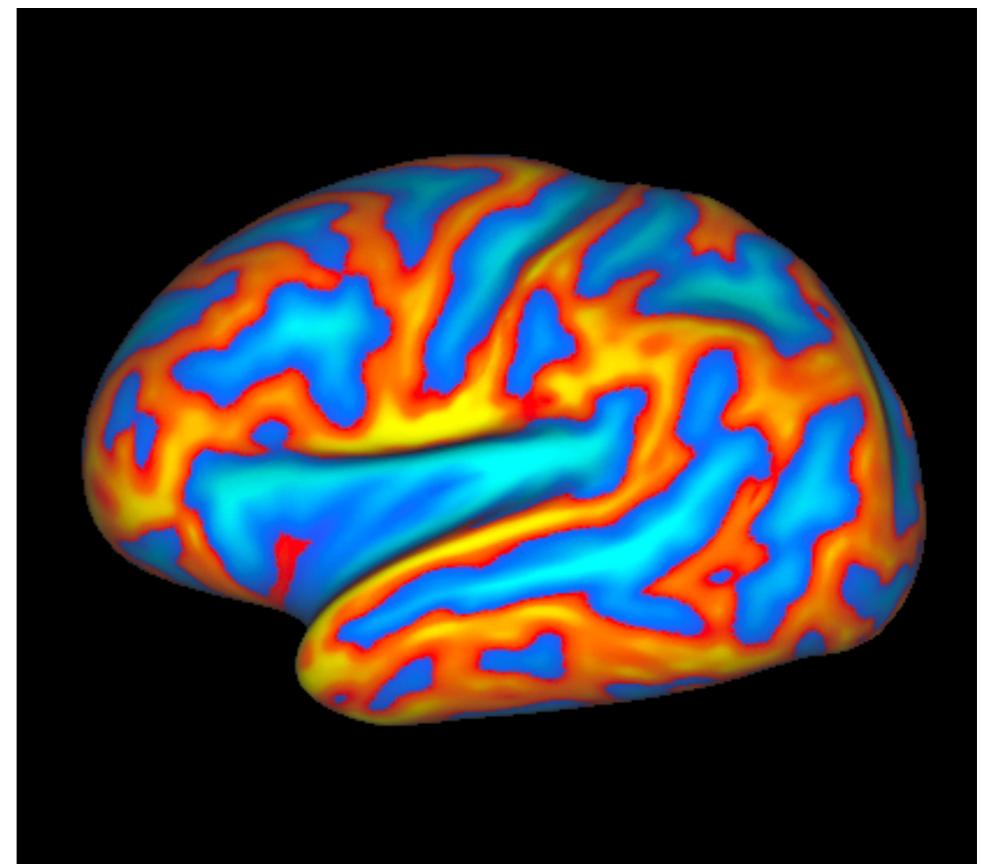
Fig. 8. Segmented T2 image intersected by white and pial surfaces (left). White boxes outline corrections in areas where CSF appears dark due to partial volume effects, and yellow boxes corrections in areas where the CSF has been mislabelled as WM. Zoom of white surface mesh before (middle) and after (right) edge-based refinement. The top row demonstrates correction of a sulcus by moving the surface inwards, and the bottom row correction of a segmentation hole by moving the surface outwards.

Features: Sulcal Depth

- Coarse scale folding patterns
- Measure of Convexity
- Derived from integration of the force used to inflate WM surface to smooth inflated surface

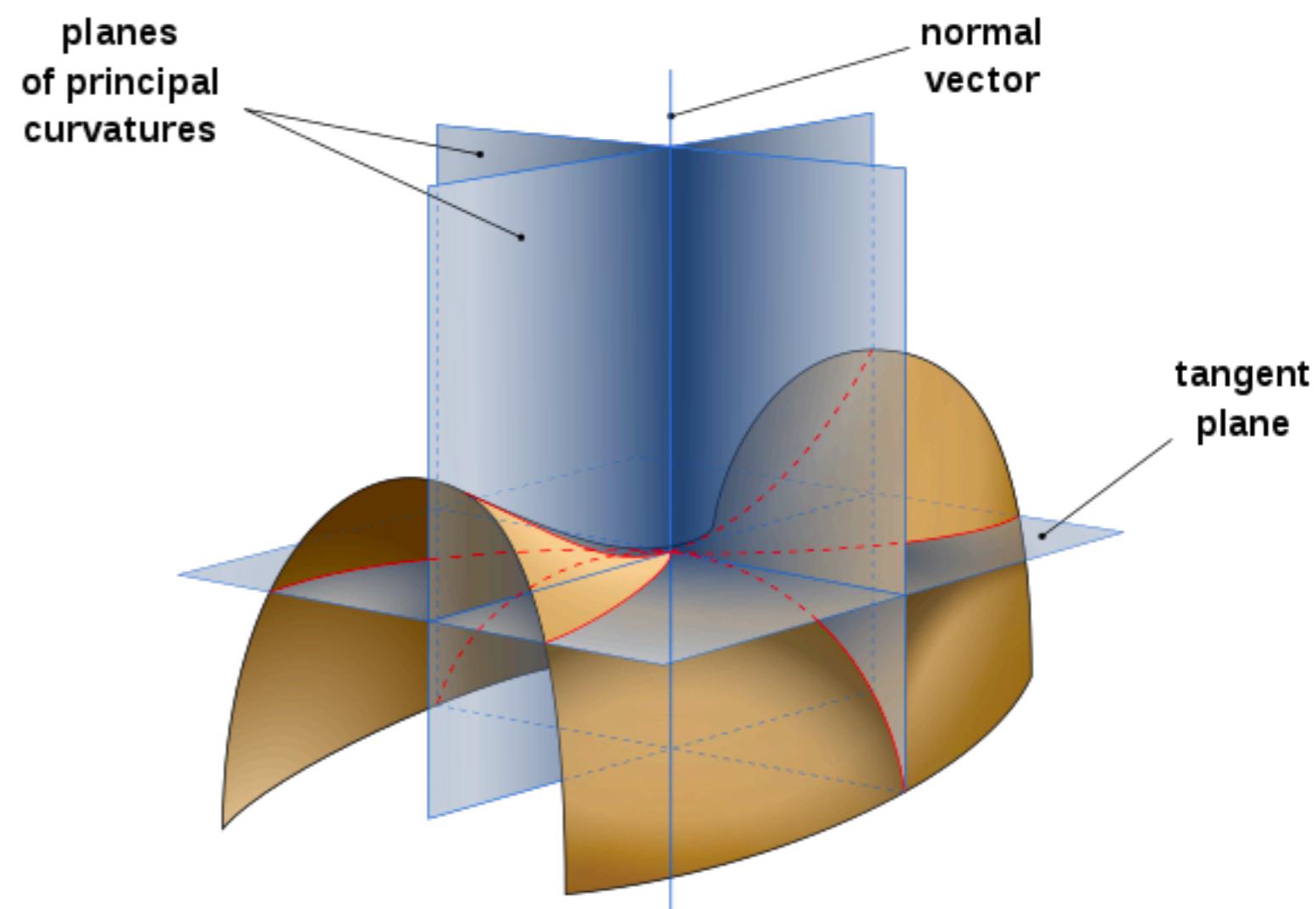
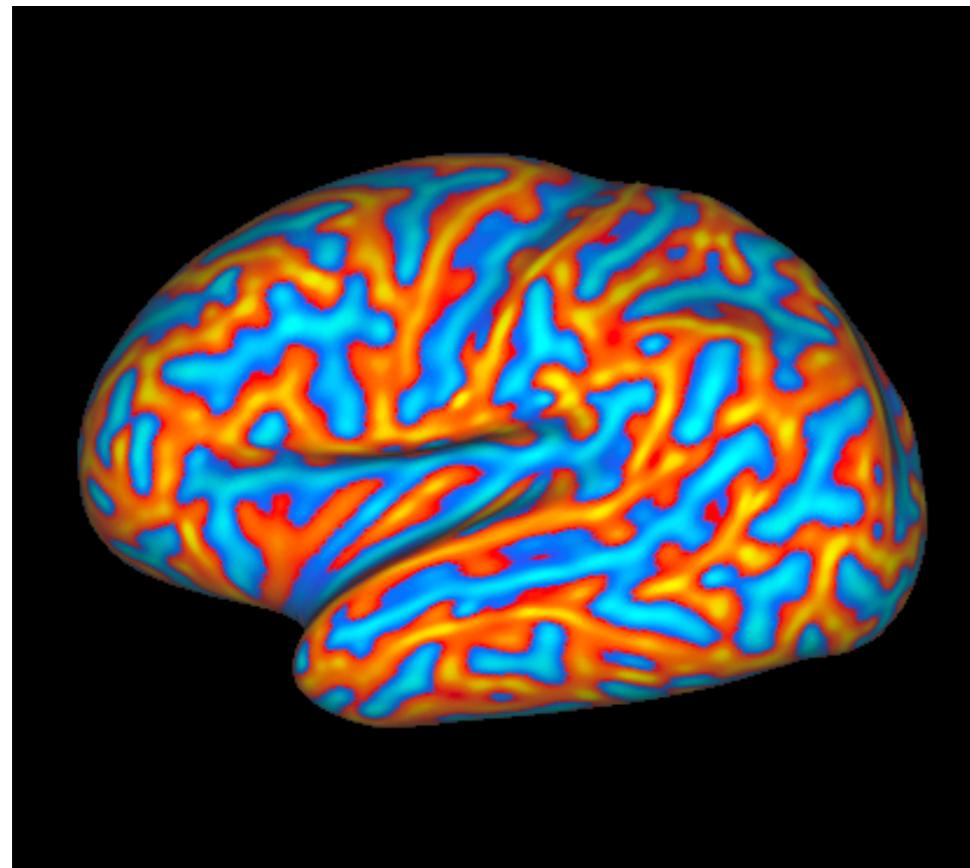
$$C(\mathbf{x}_k^0) = \int \left(\frac{\partial J_s}{\partial \mathbf{x}_k^t} \cdot \mathbf{n}(k) \right) dt,$$

$$J_s = \frac{1}{2V} \left(\sum_{i=1}^V \sum_{n \in N_1(i)} \|\mathbf{x}_i - \mathbf{x}_n\|^2 \right) + \lambda_d J_d,$$



Features: Curvature

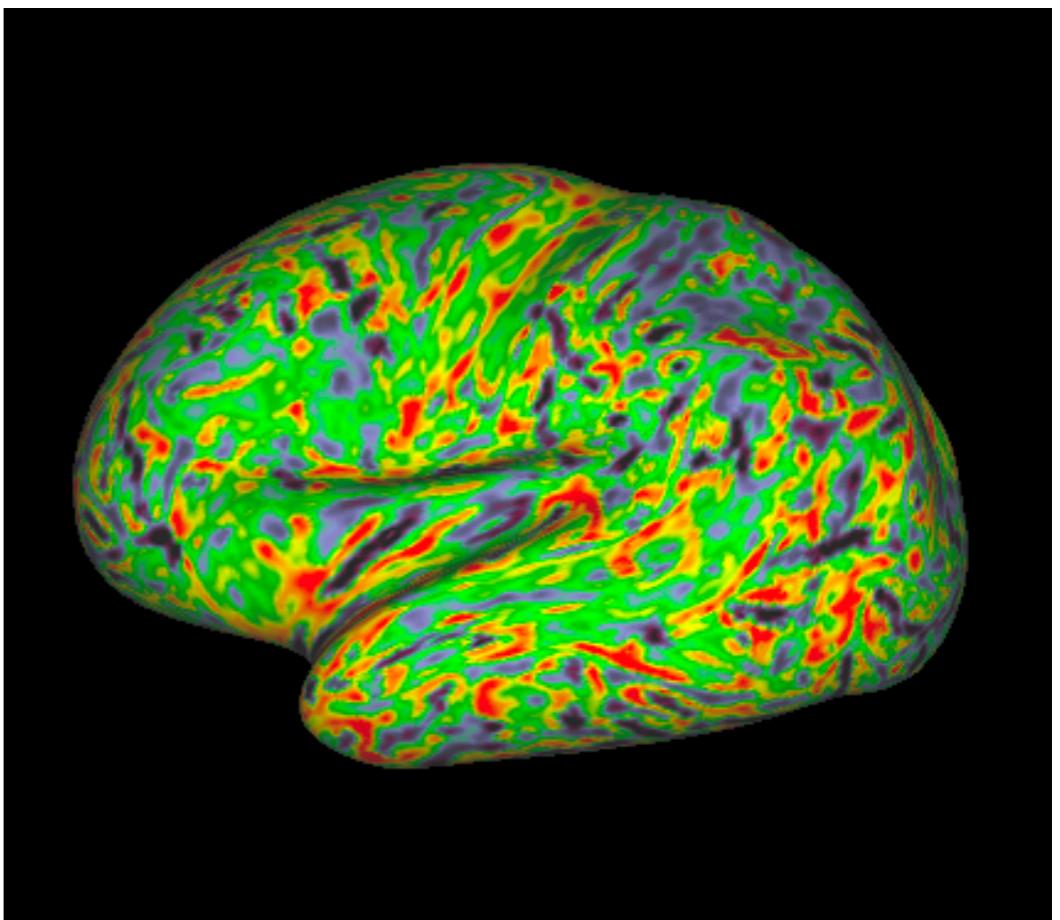
- two **principal curvatures** are the **eigenvalues** of the shape operator at the point
- Feature map generated from mean



Saddle surface with normal planes
in directions of principal curvatures

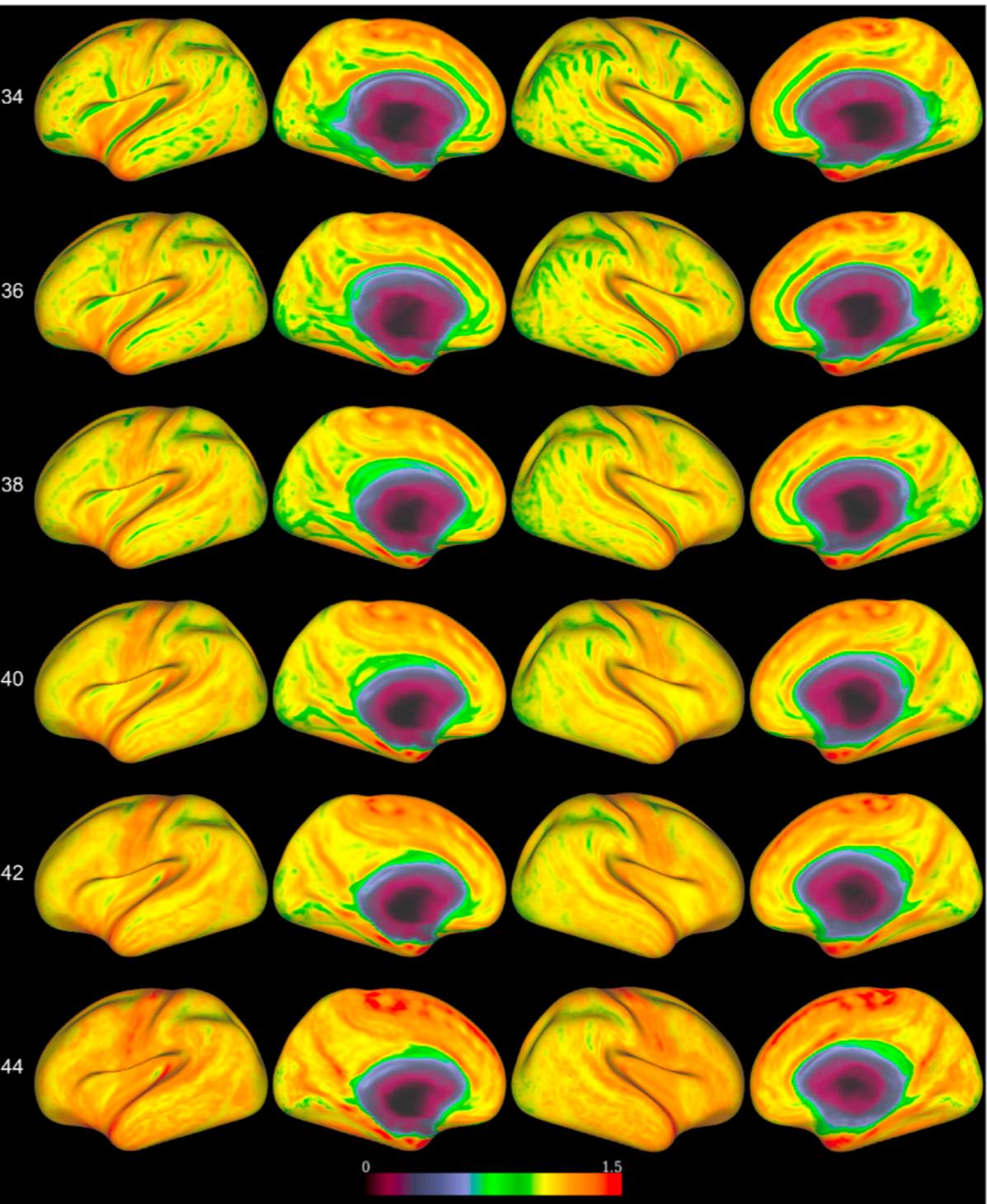
Features: Thickness

- Distance between the cortical white and cortical grey (pial) surfaces
- Estimated as mean Euclidean distance of white surface to the closest vertex on the pial (and vice versa)
- Cortical thickness across the whole brain shows a mean value of 1.1 mm, which increases with age (agrees with literature)



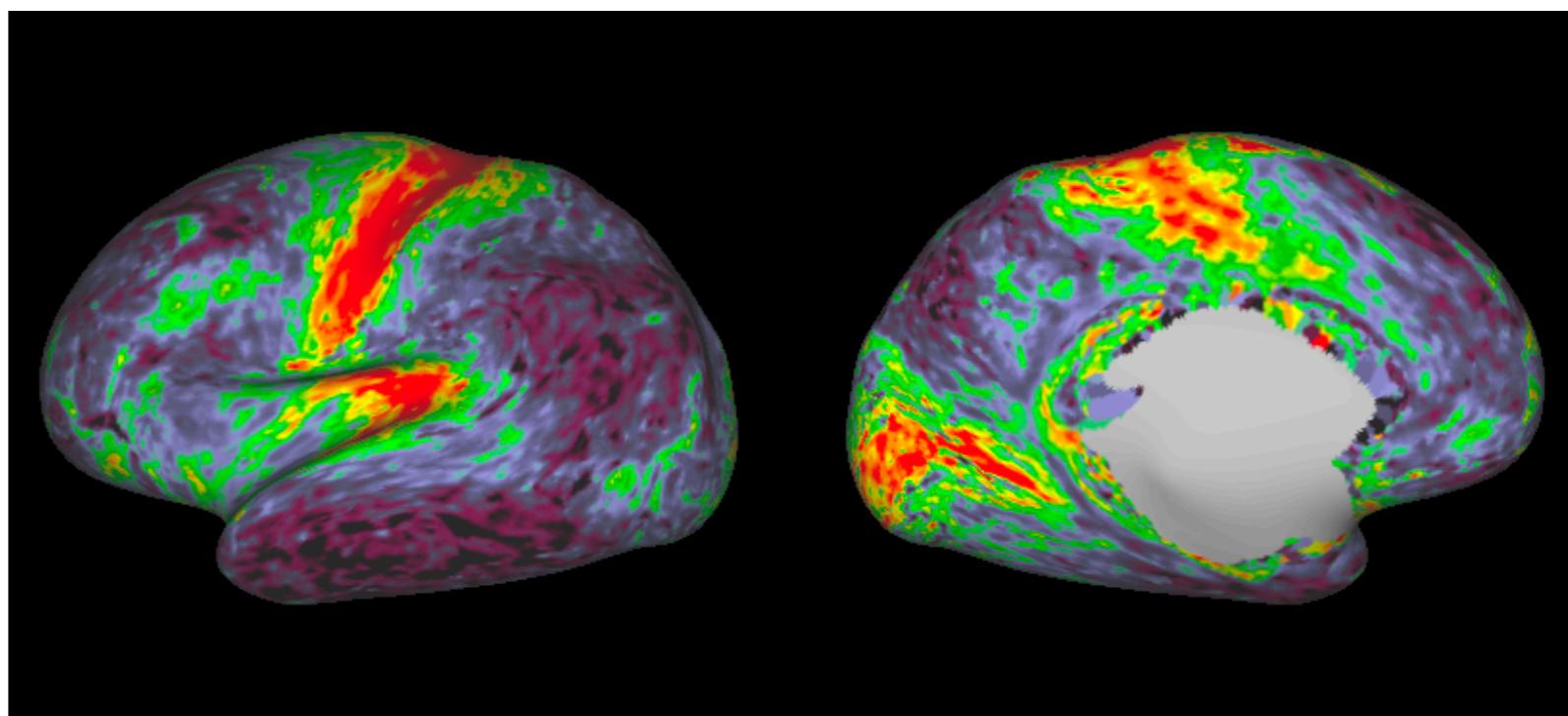
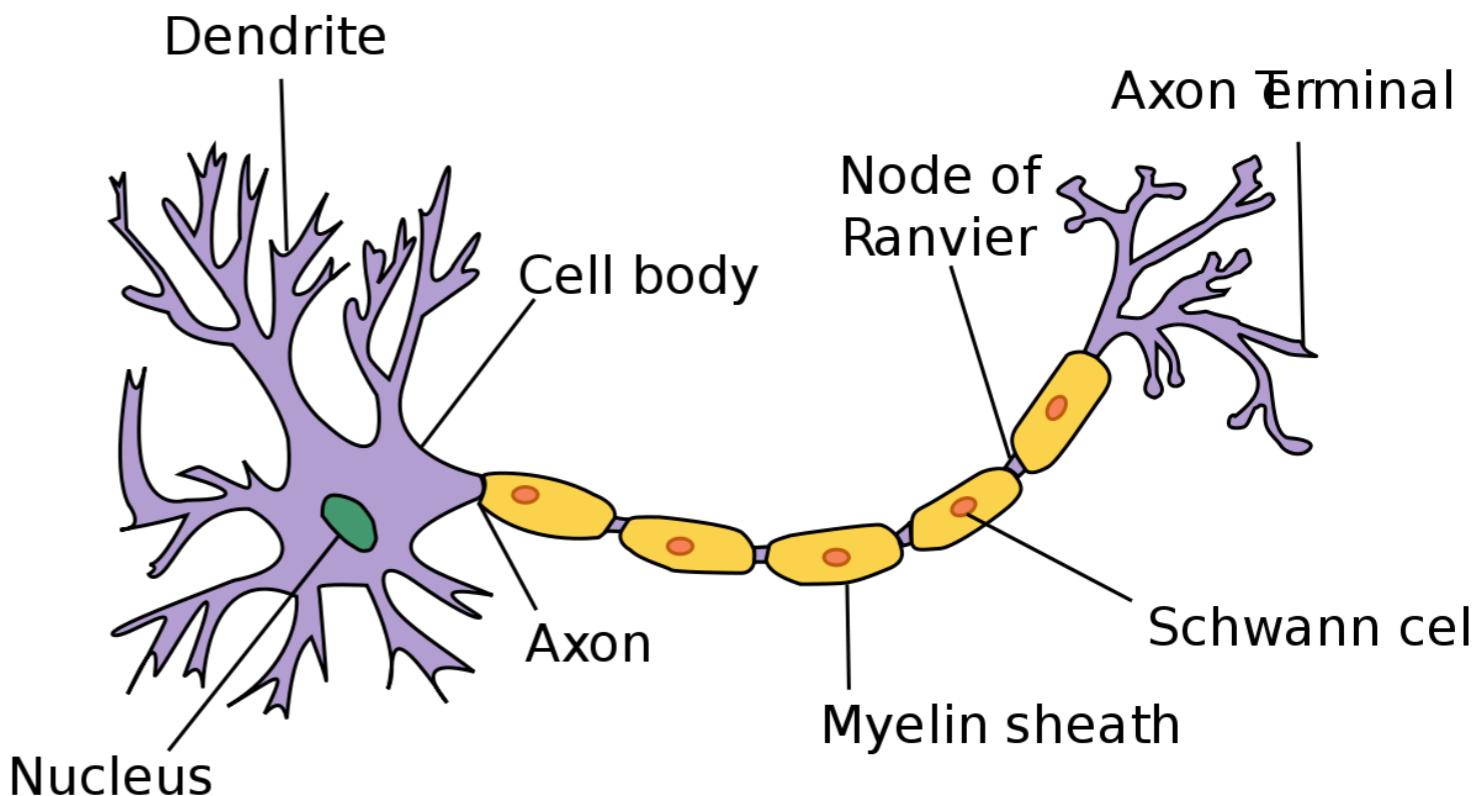
Features: Thickness

- Distance between the cortical white and cortical grey (pial) surfaces
- Estimated as mean Euclidean distance of white surface to the closest vertex on the pial (and vice versa)
- Cortical thickness across the whole brain shows a mean value of 1.1 mm, which increases with age (agrees with literature)



Features: Myelin

- Cortex has many layers
- Cortical myelin reflects nerve bundles that
 - Reflect long distance connections
 - Are highly myelinated
 - Project to/from highest layers of cortex



Neonatal Volume QC

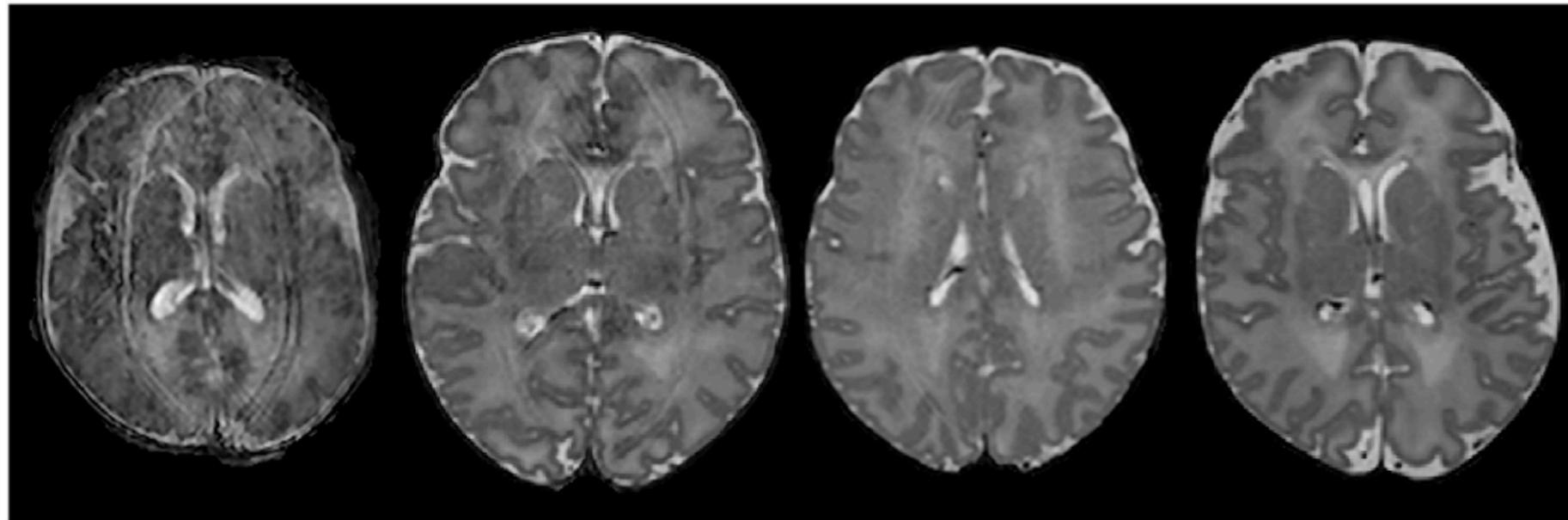


Fig. 13. Manual QC score of image quality. From left to right: poor image quality - score 1, significant motion - score 2, negligible motion - score 3, good quality image - score 4.

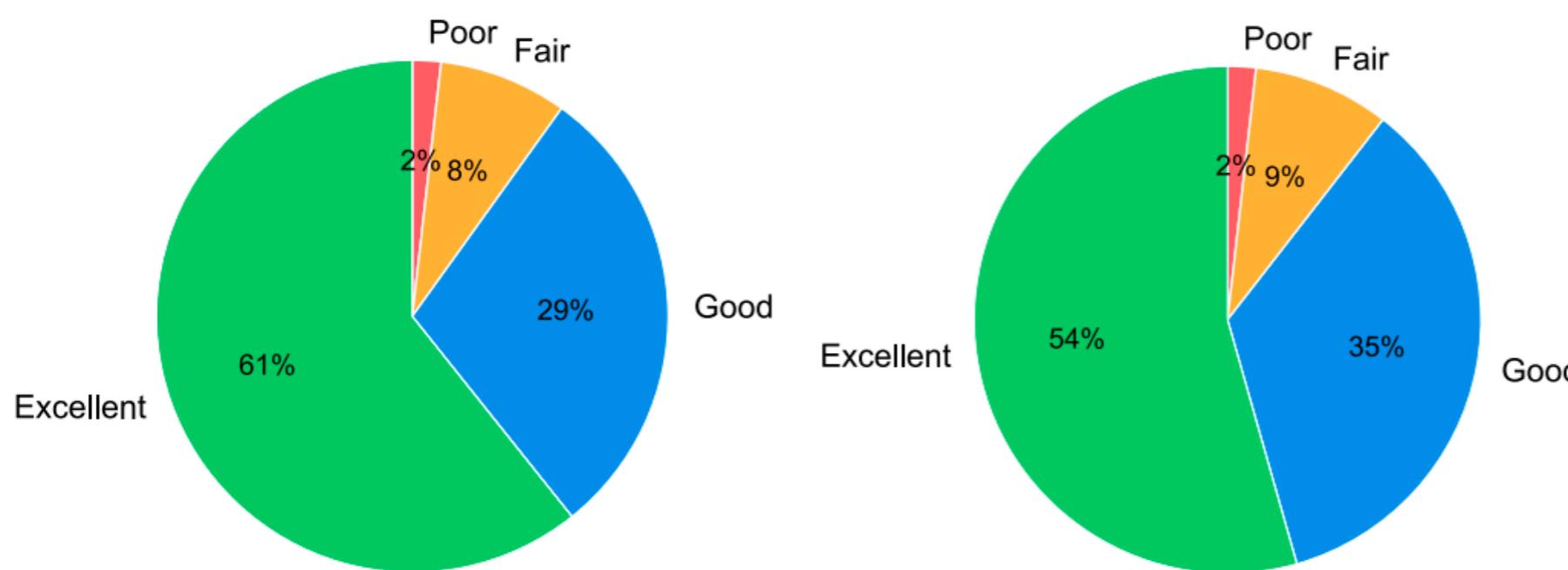


Fig. 14. Image scores from the 2 raters (based on 160 images).

Neonatal Volume QC

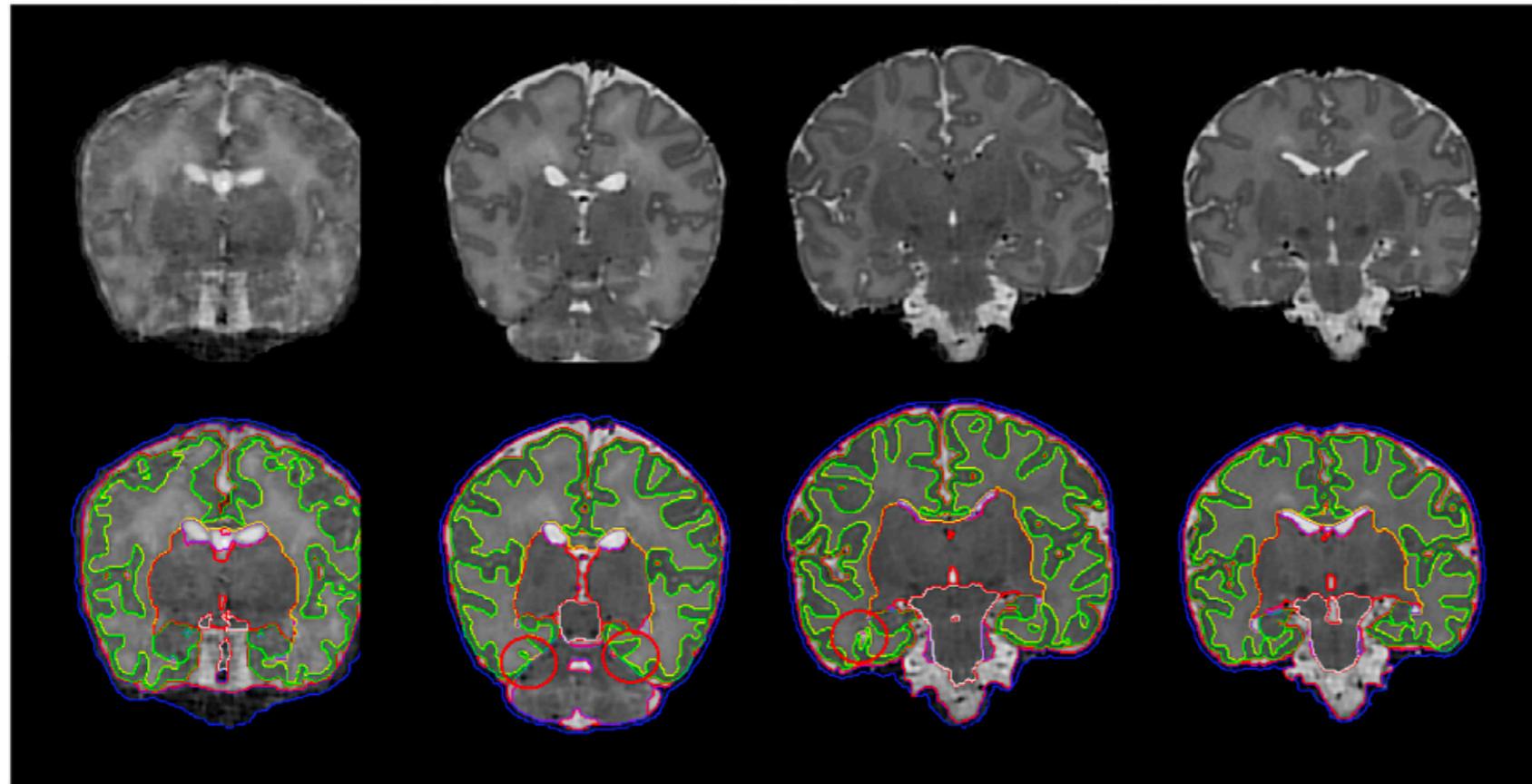


Fig. 15. Manual QC score of segmentation quality. From left to right: poor segmentation quality - score 1, regional errors - score 2, localised errors - score 3, good quality segmentation - score 4.

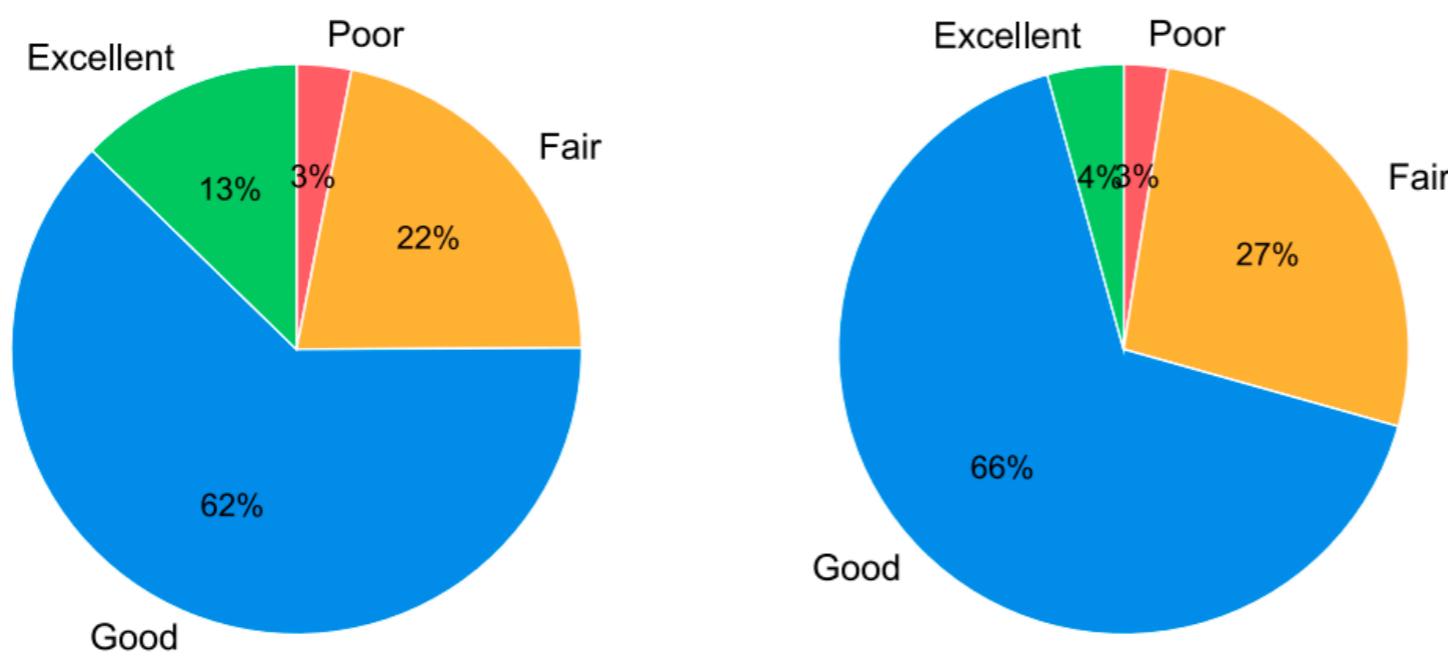


Fig. 16. Segmentation scores from the 2 raters (based on 160 images).

Neonatal Volume QC

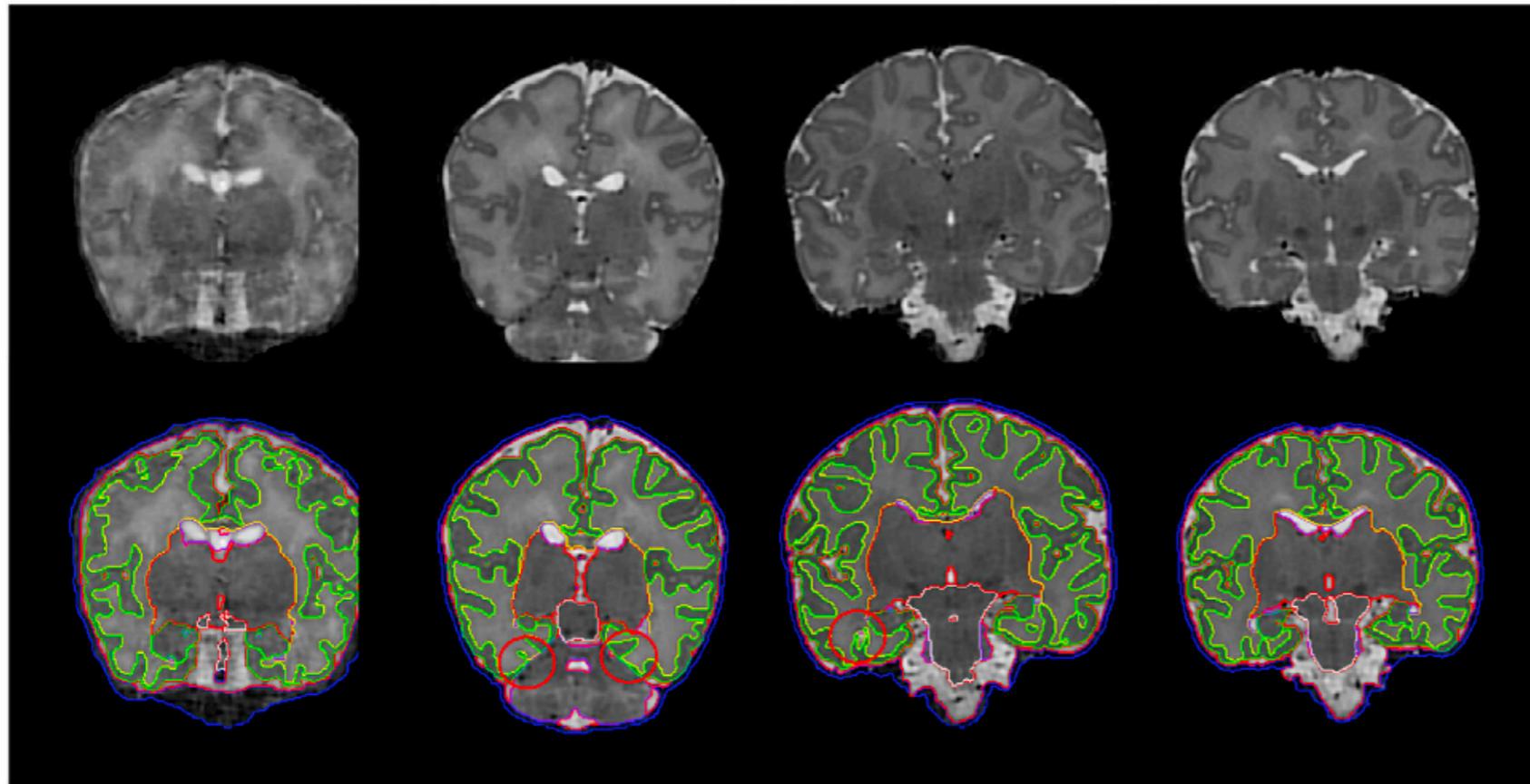
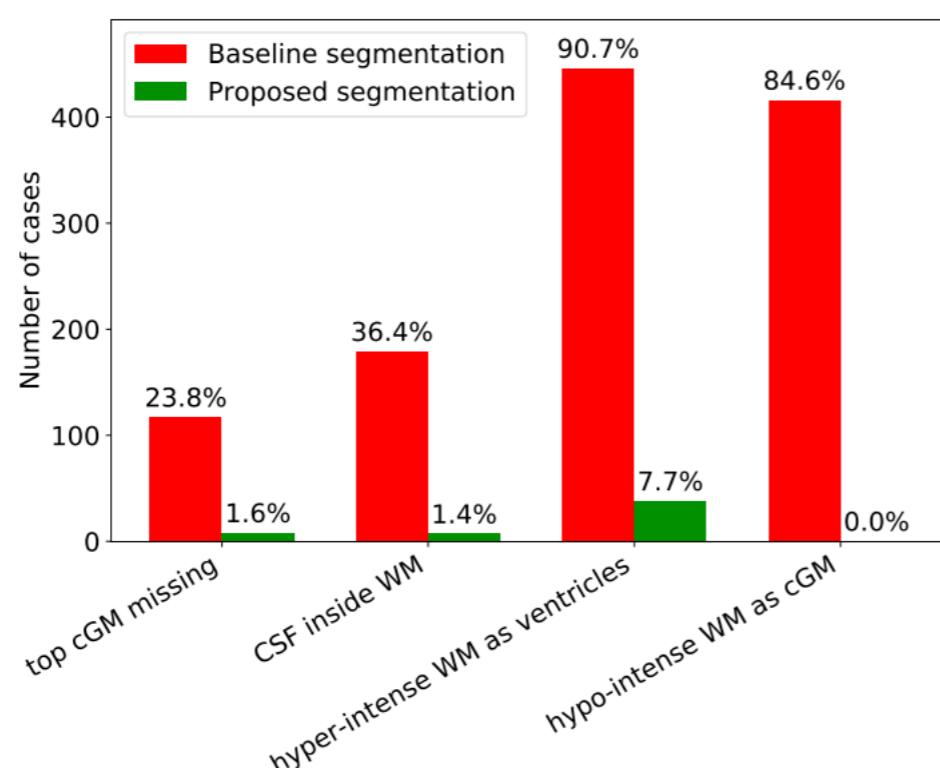


Fig. 15. Manual QC score of segmentation quality. From left to right: poor segmentation quality - score 1, regional errors - score 2, localised errors - score 3, good quality segmentation - score 4.

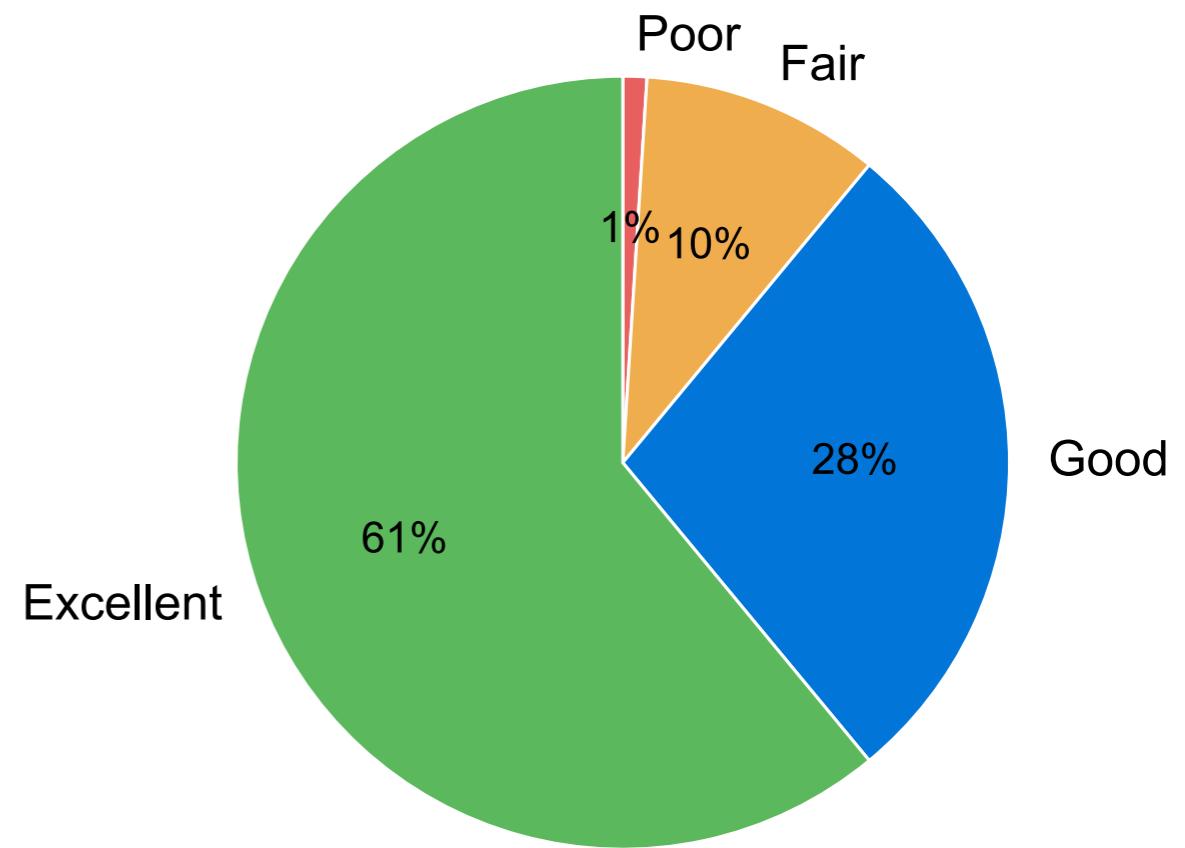


Neonatal Surface QC

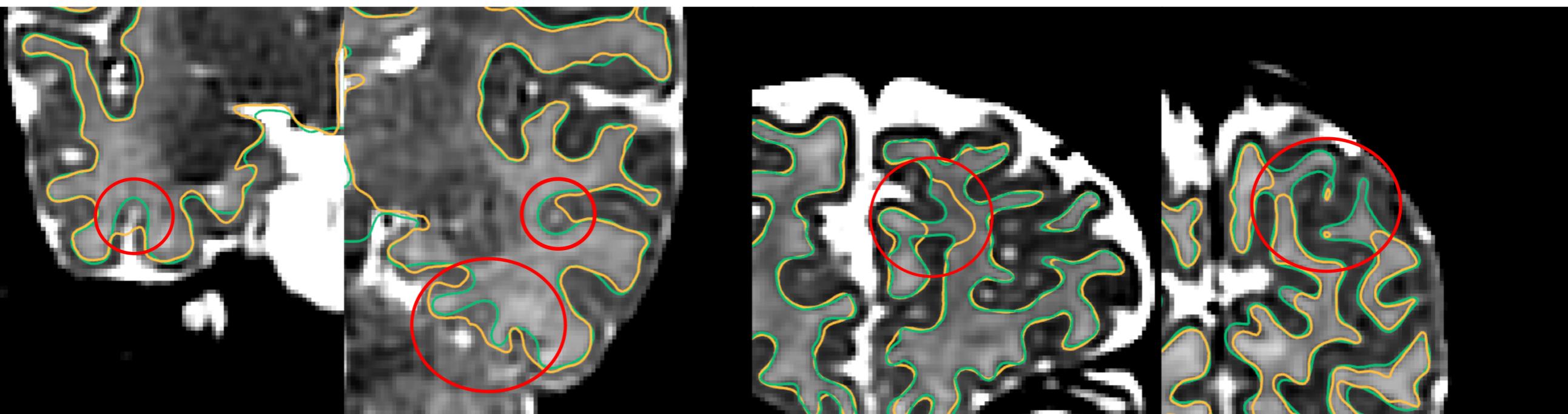
2 raters rated

- 43 images
- Patches of size 50x50x50mm
- White surface only

Example QC from single rater

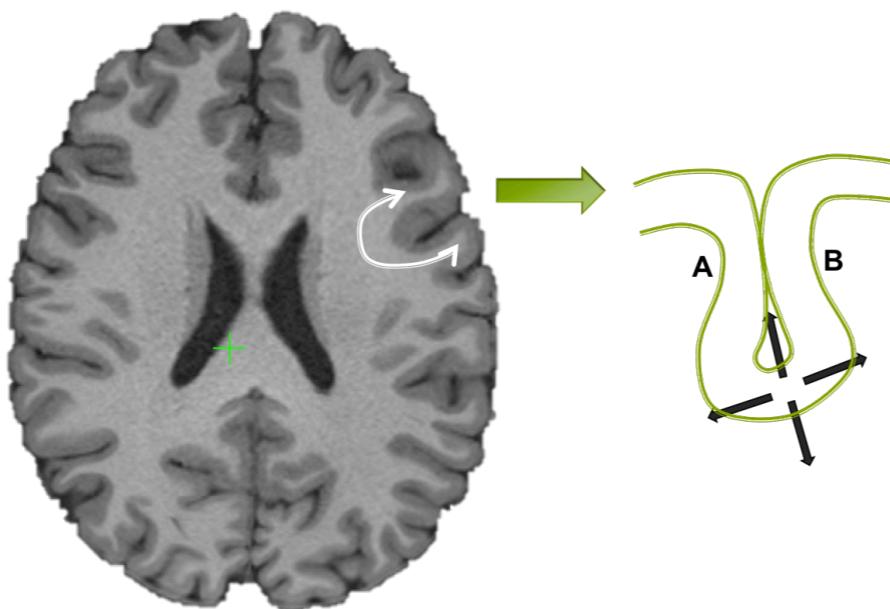


Comparison of intensity-based surface refinement (green) to segmentation result (yellow)

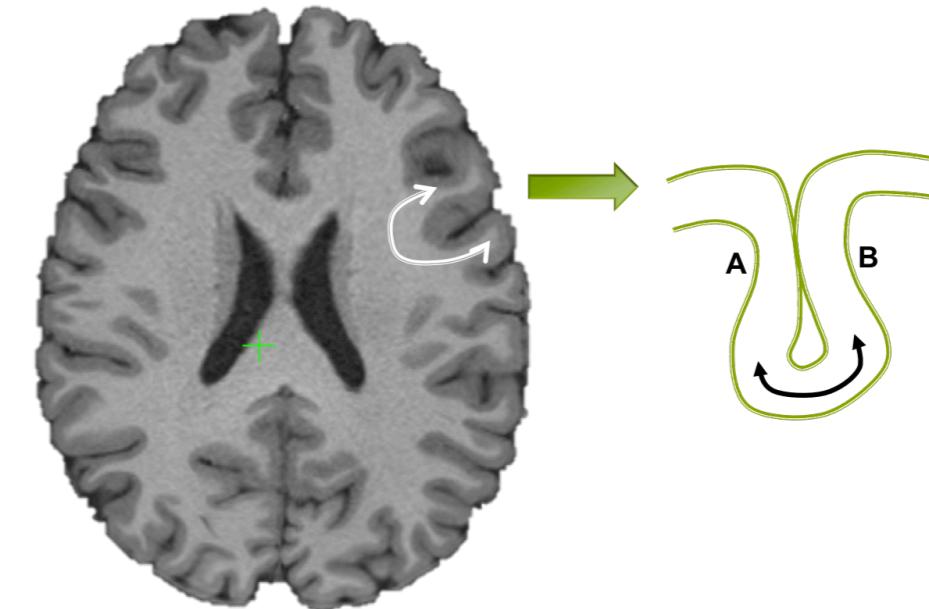


Why work with surfaces?

1. Surface based smoothing improves SNR
2. Surface-based registration improves alignment of cortical folds



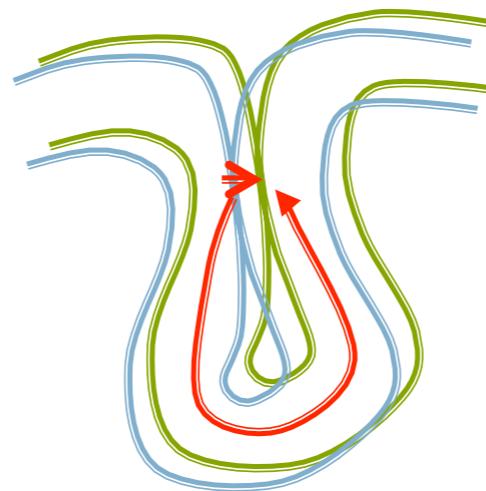
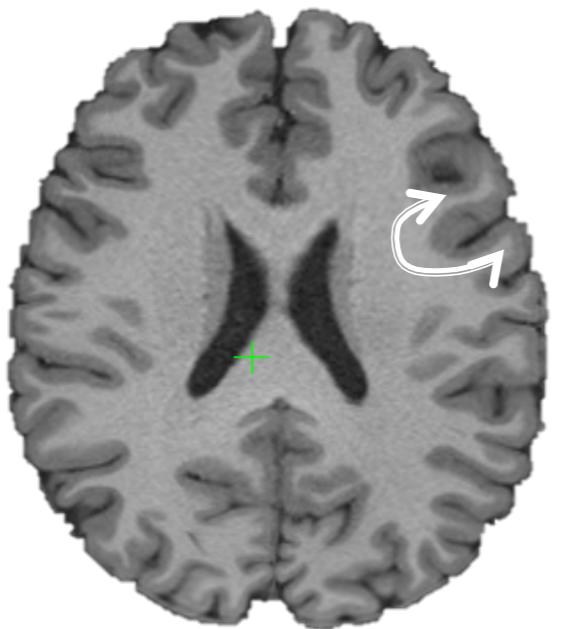
Volumetric smoothing mixes signals



Surface-constrained smoothing averages only GM signals

Why work with surfaces?

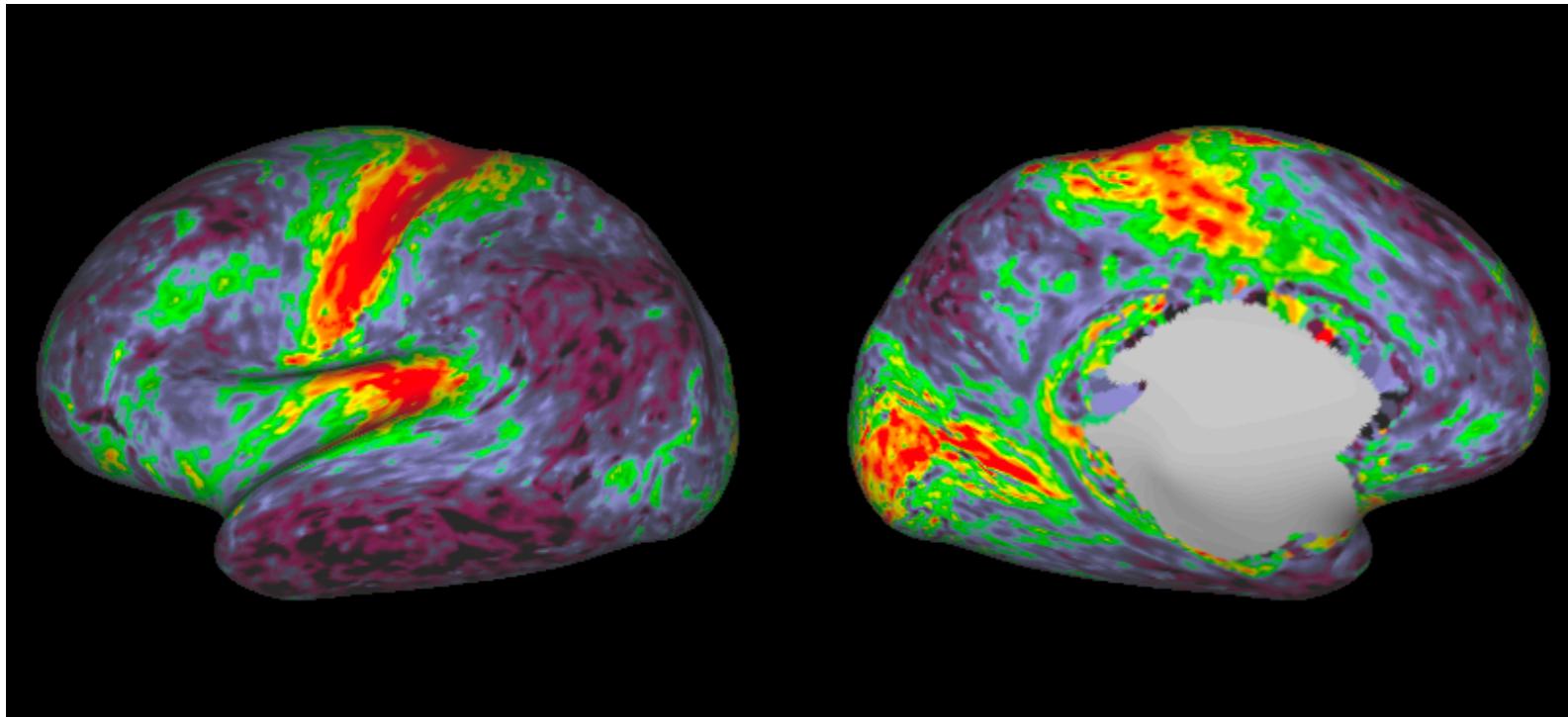
1. Surface based smoothing improves SNR
2. Surface-based registration improves alignment of cortical folds



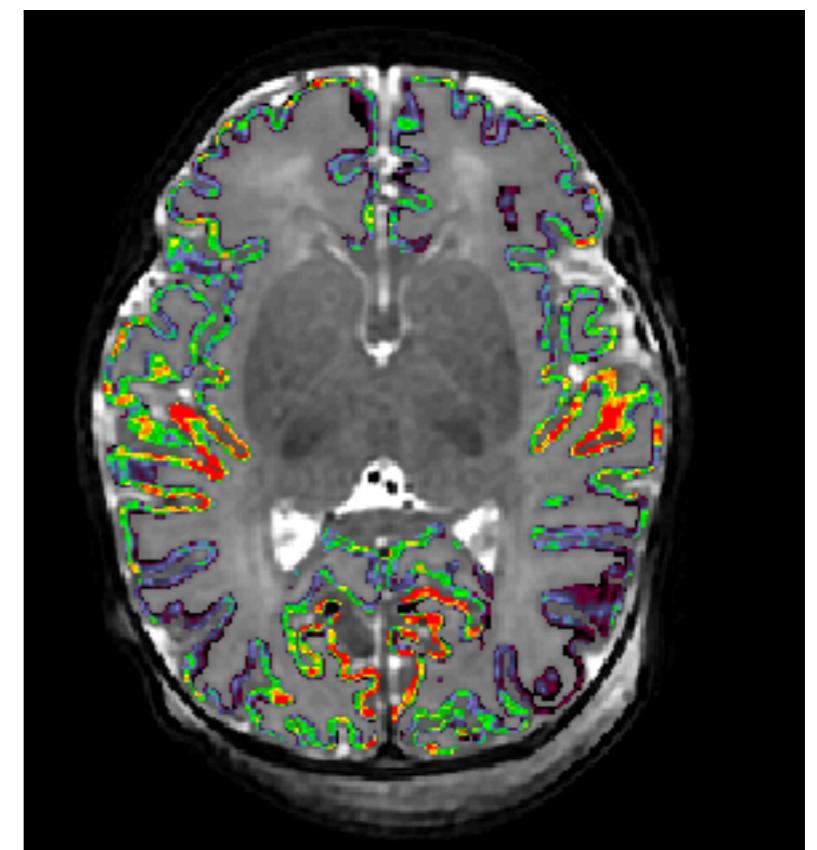
Small mis-registrations in 3D can have a large impact on the alignment of the cortical sheet

Why work with surfaces?

1. Surface based smoothing improves SNR
2. Surface-based registration improves alignment of cortical folds
3. Clearer representation for variation of cortical features.

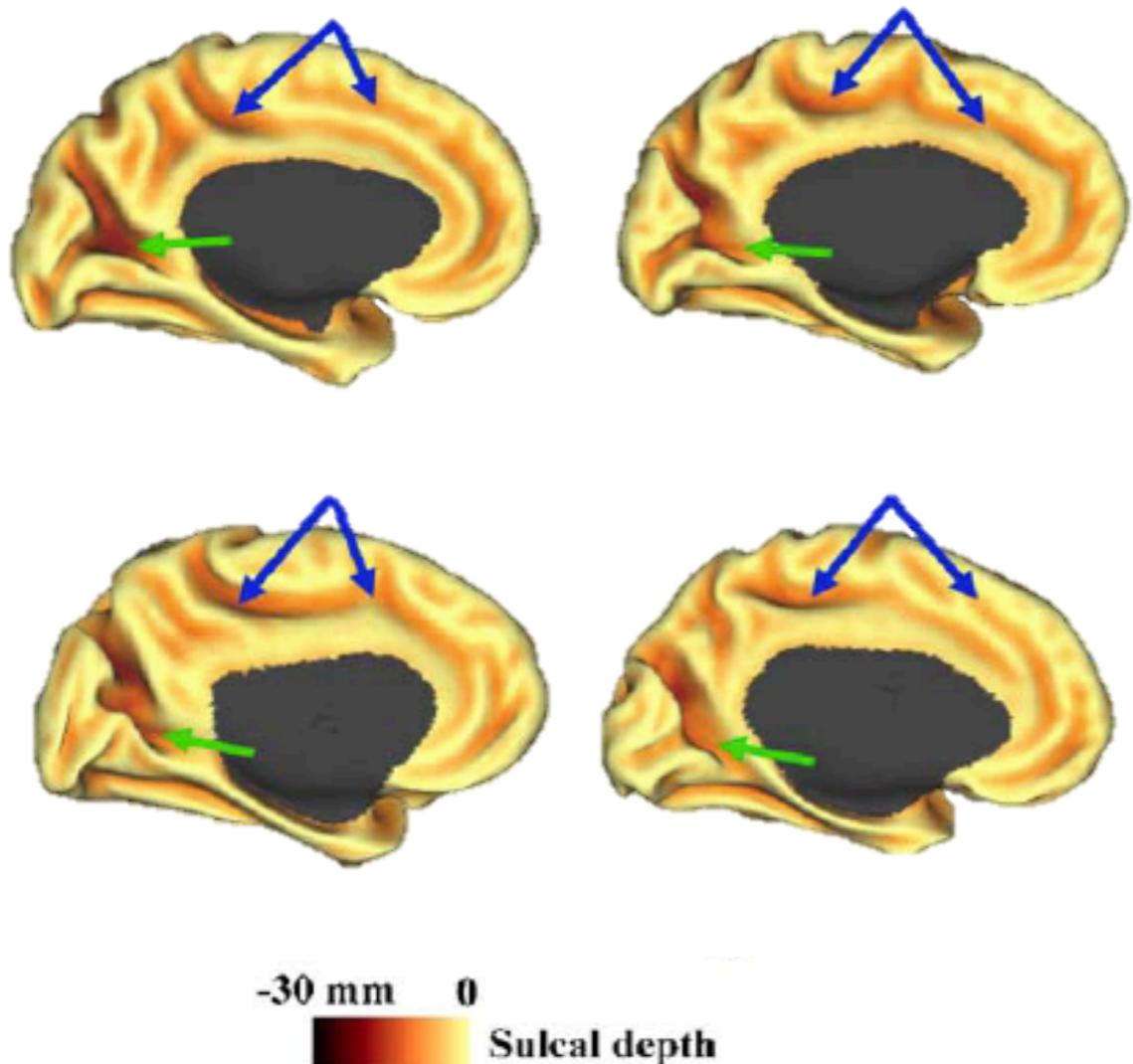


Surface (cortical) myelin



Volume (cortical) myelin

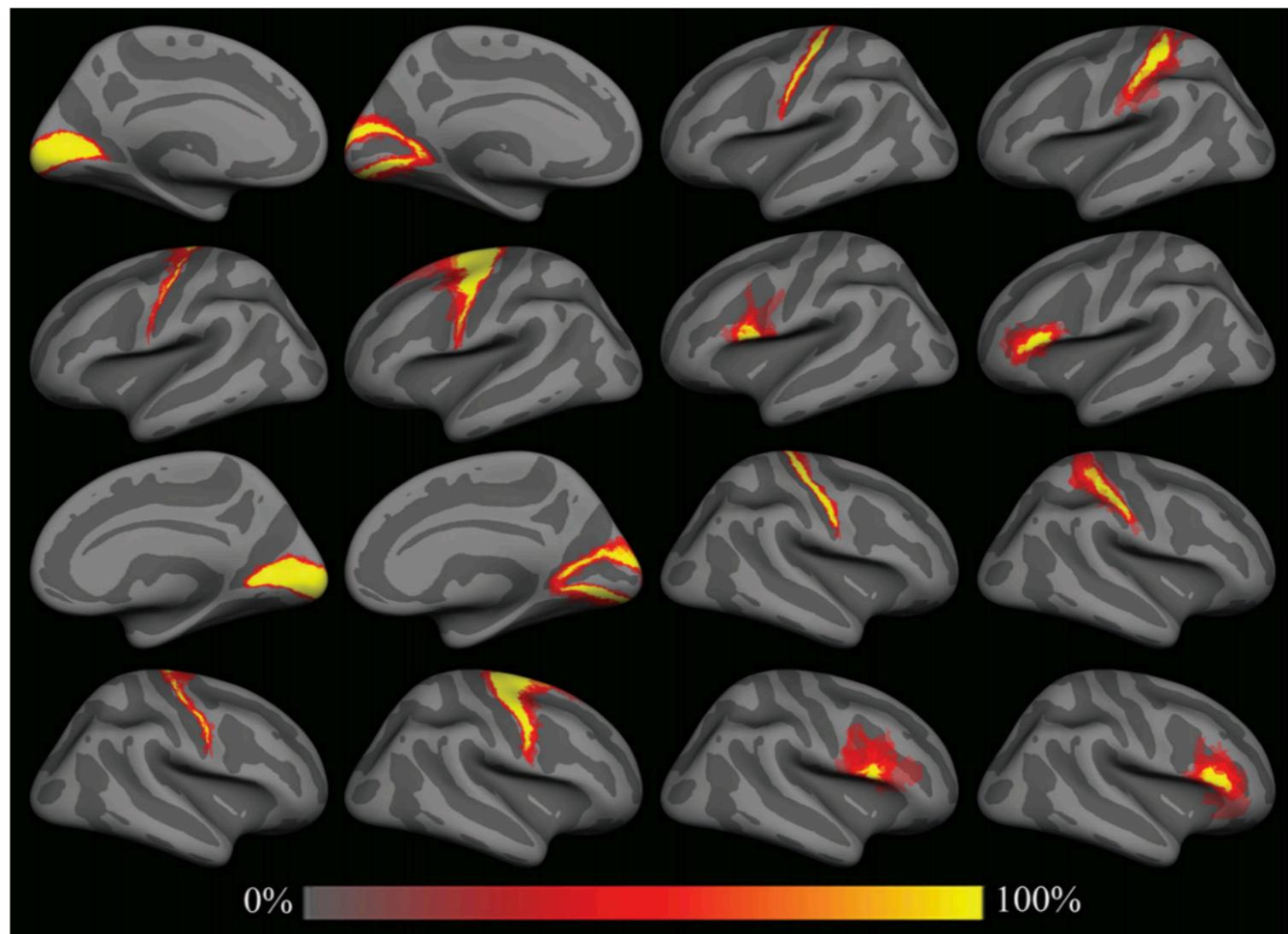
Limitations of morphological alignment



- Cortical folding patterns are highly variable across subjects
- Example: Cingulate (blue arrows)
- Some subjects have one fold where others have two
- Courtesy of Van Essen, NeuroImage 28 (2005) 635 – 662

Limitations of morphological alignment

- Alignment by cortical folds can lead to high residual variability of functional regions across subjects

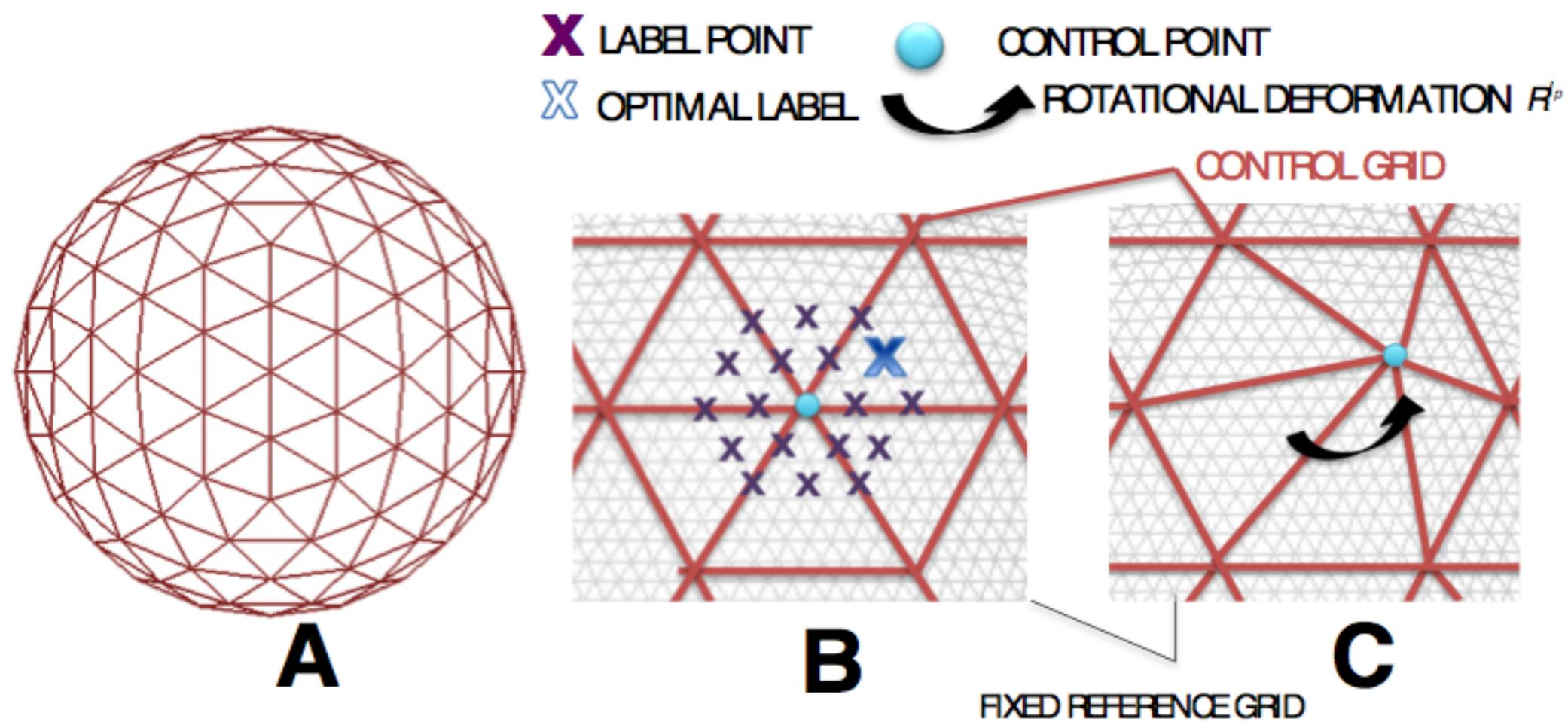


Surface-based alignment: MSM

- Spherical framework for cortical surface registration
- Use low resolution control point grids to constrain the deformation
- Optimised using discrete methods
- Modular

Surface-based alignment: MSM

- Spherical framework for cortical surface registration
- Use low resolution control point grids to constrain the deformation
- Optimised using discrete methods
- Modular



Surface-based alignment: MSM

- Spherical framework for cortical surface registration
- Use low resolution control point grids to constrain the deformation
- Optimised using discrete methods
- Modular

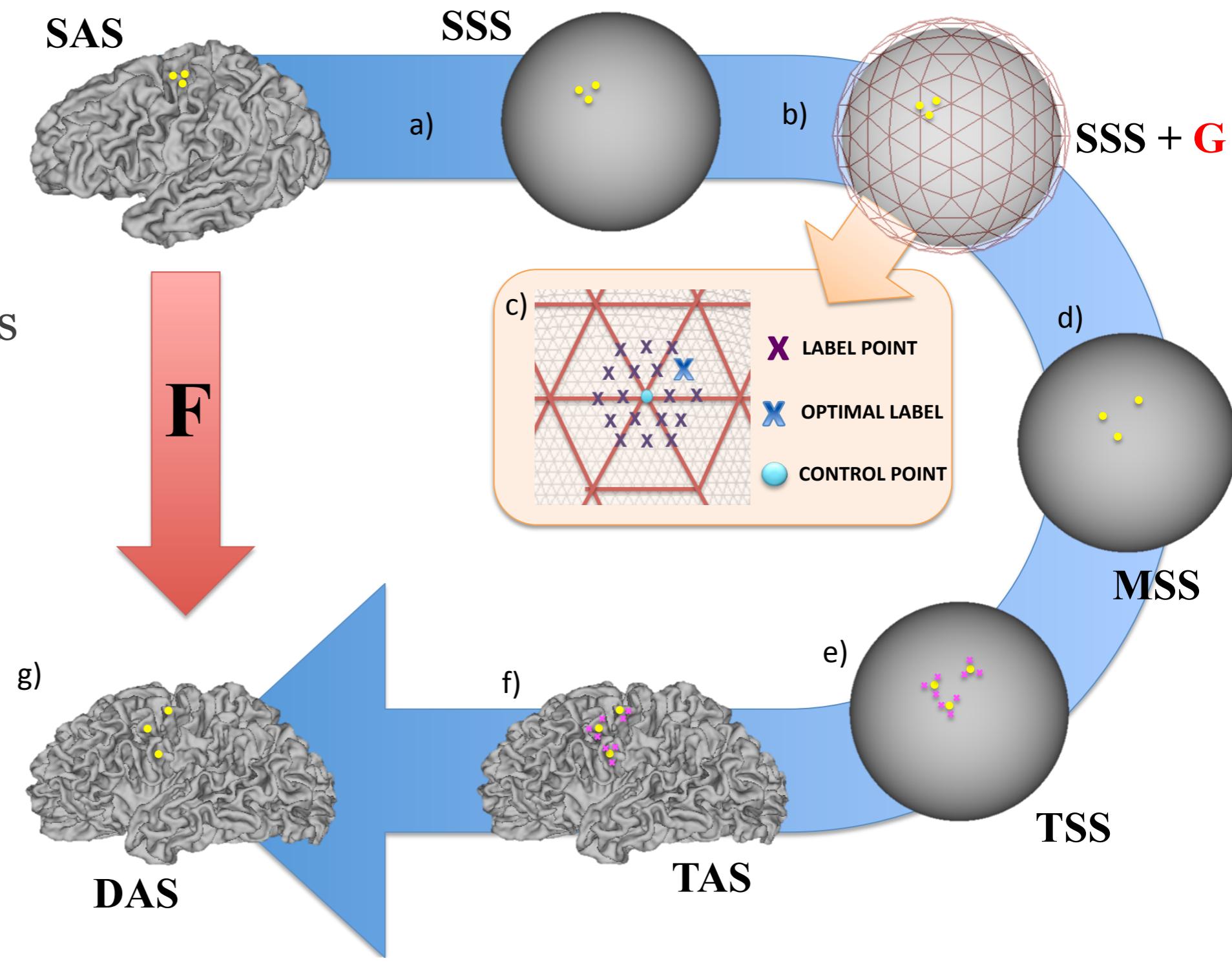
data cost: i.e. correlation, MNI, SSD

$$\min C(\mathbf{l}) = \sum_{c_1 \in C_D} c(\mathbf{l}_{c_1}) + \sum_{c_2 \in C_R} \lambda V(\mathbf{l}_{c_2})$$

Regularisation cost to encourage smoother warp

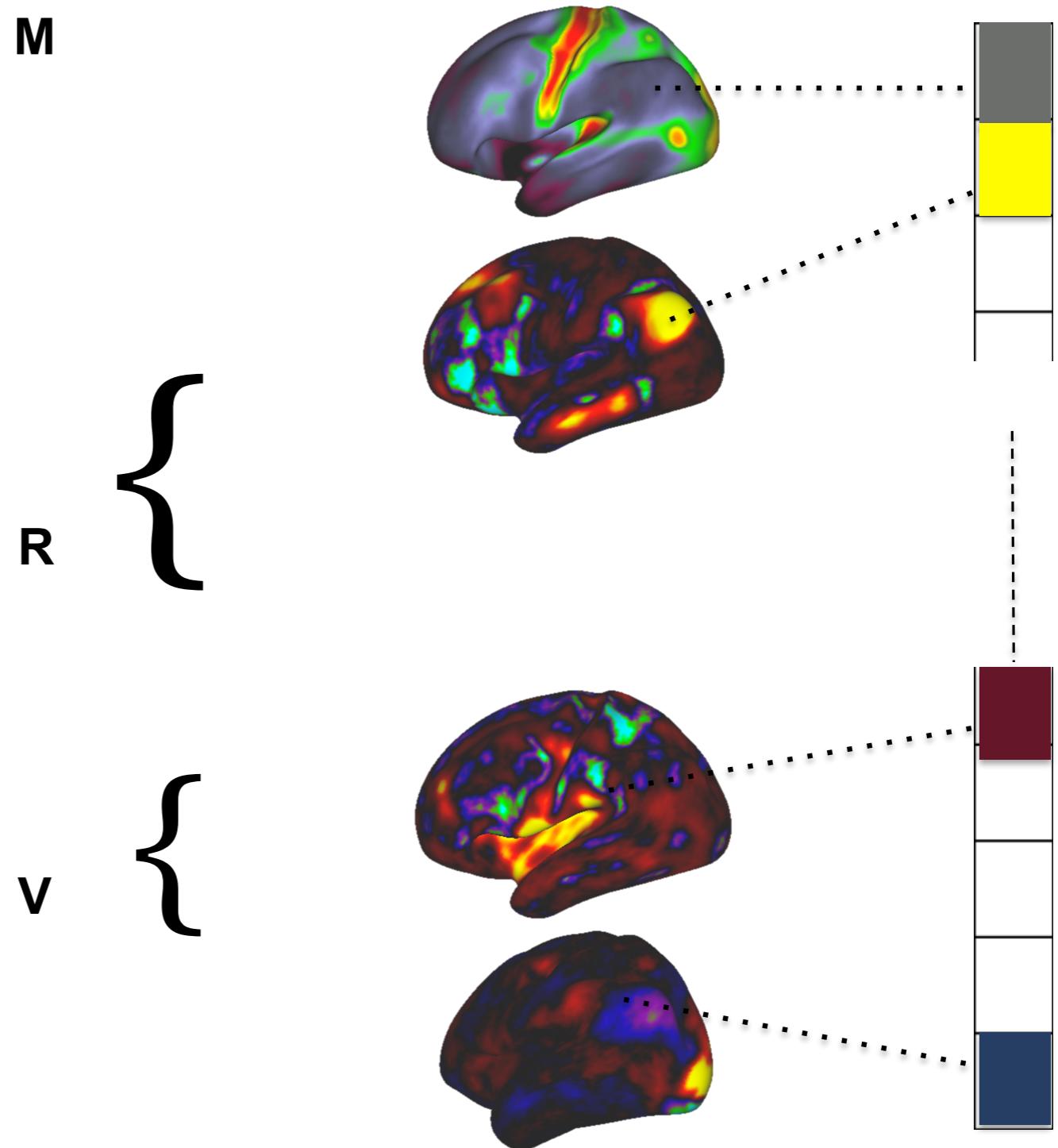
Finding trends in longitudinal cortical development

MSM now also allows smooth deformation of cortical anatomies



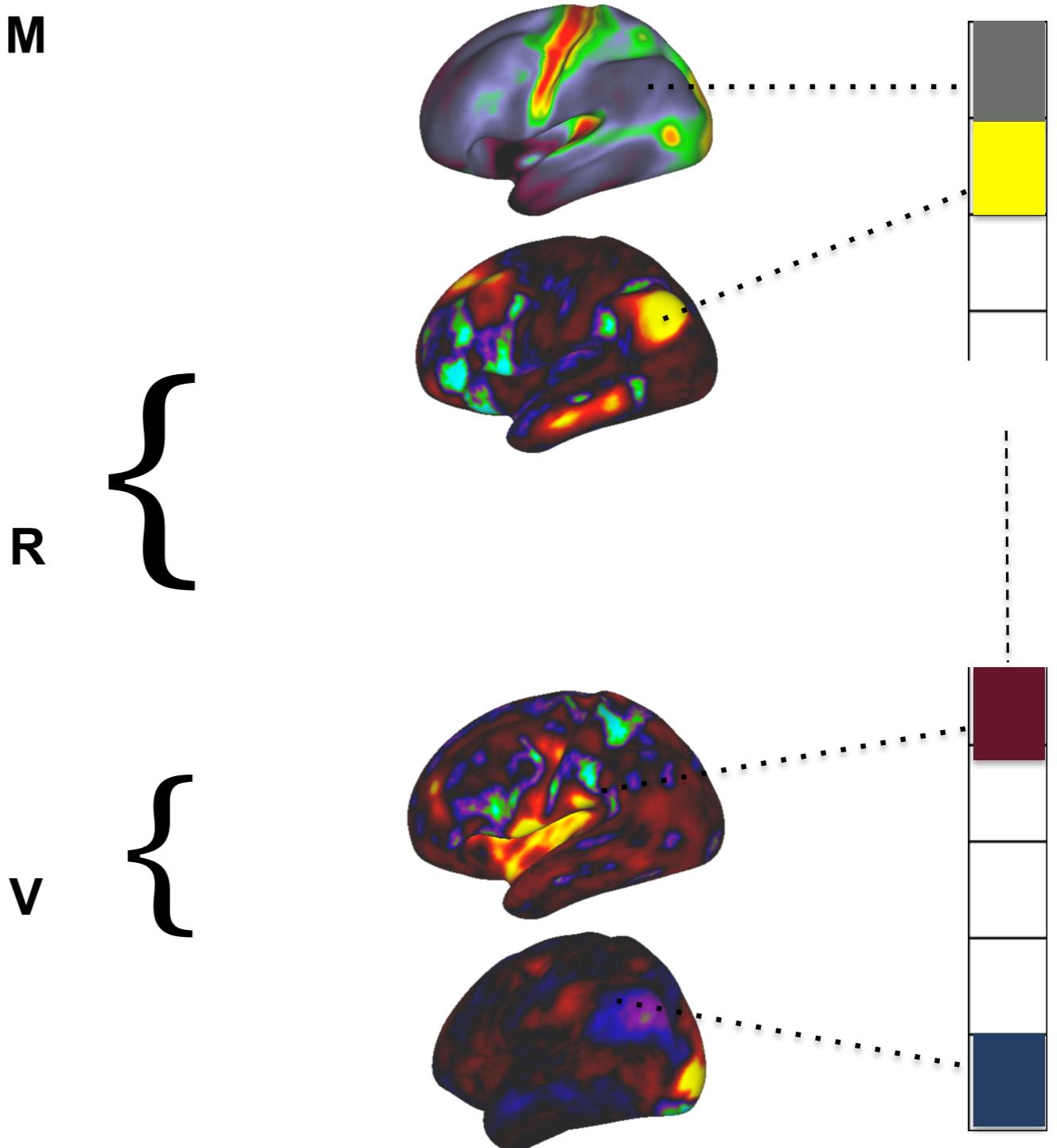
Robinson, Emma C., et al.
"Multimodal surface matching with higher-order smoothness constraints." *NeuroImage* (2018).

MSM: improves alignment of areal features



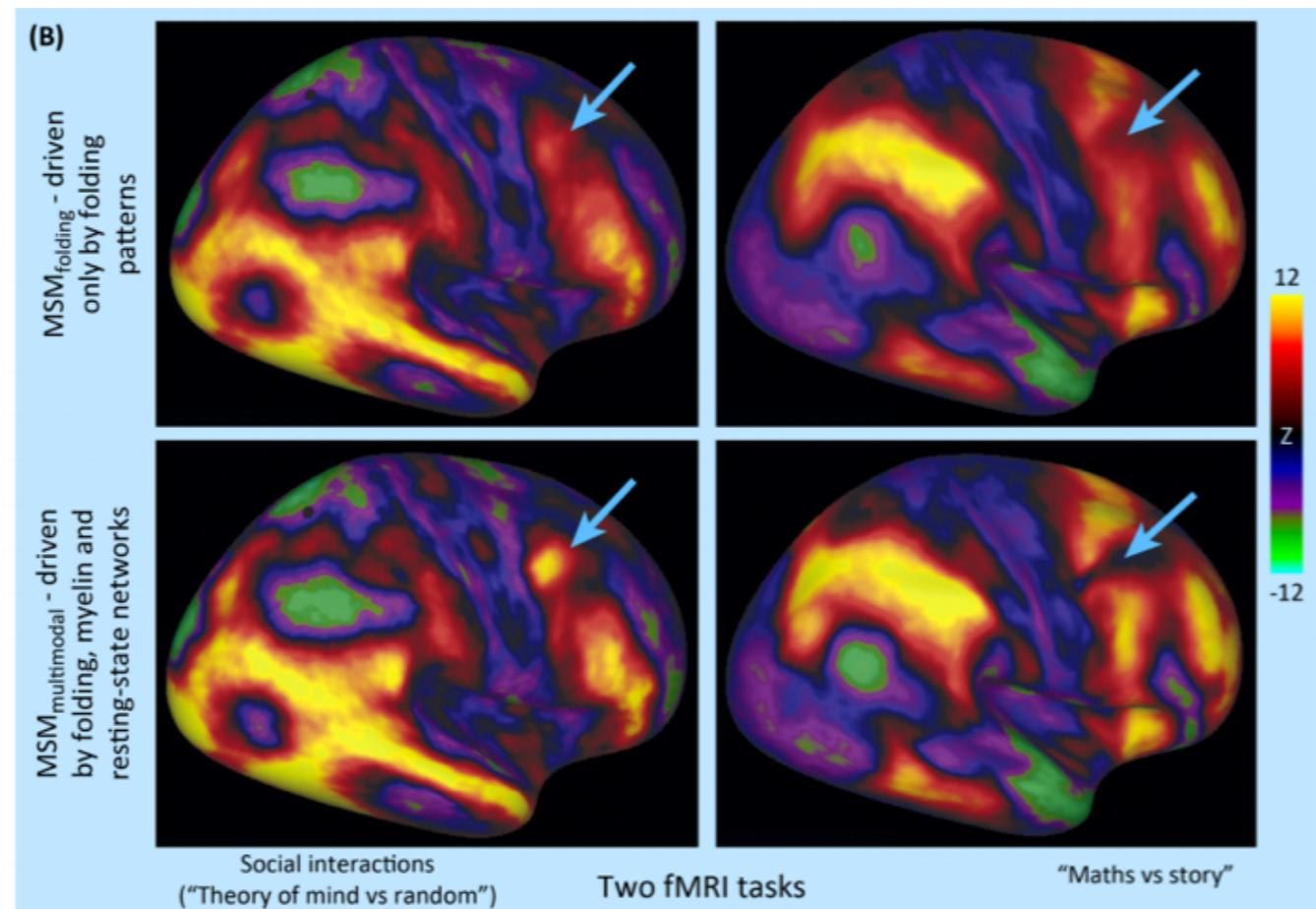
MSM: improves alignment of areal features

- Alignment driven multivariate feature vectors
 - ▶ myelin (M)
 - ▶ rfMRI (R)
 - ▶ visuotopic (V))



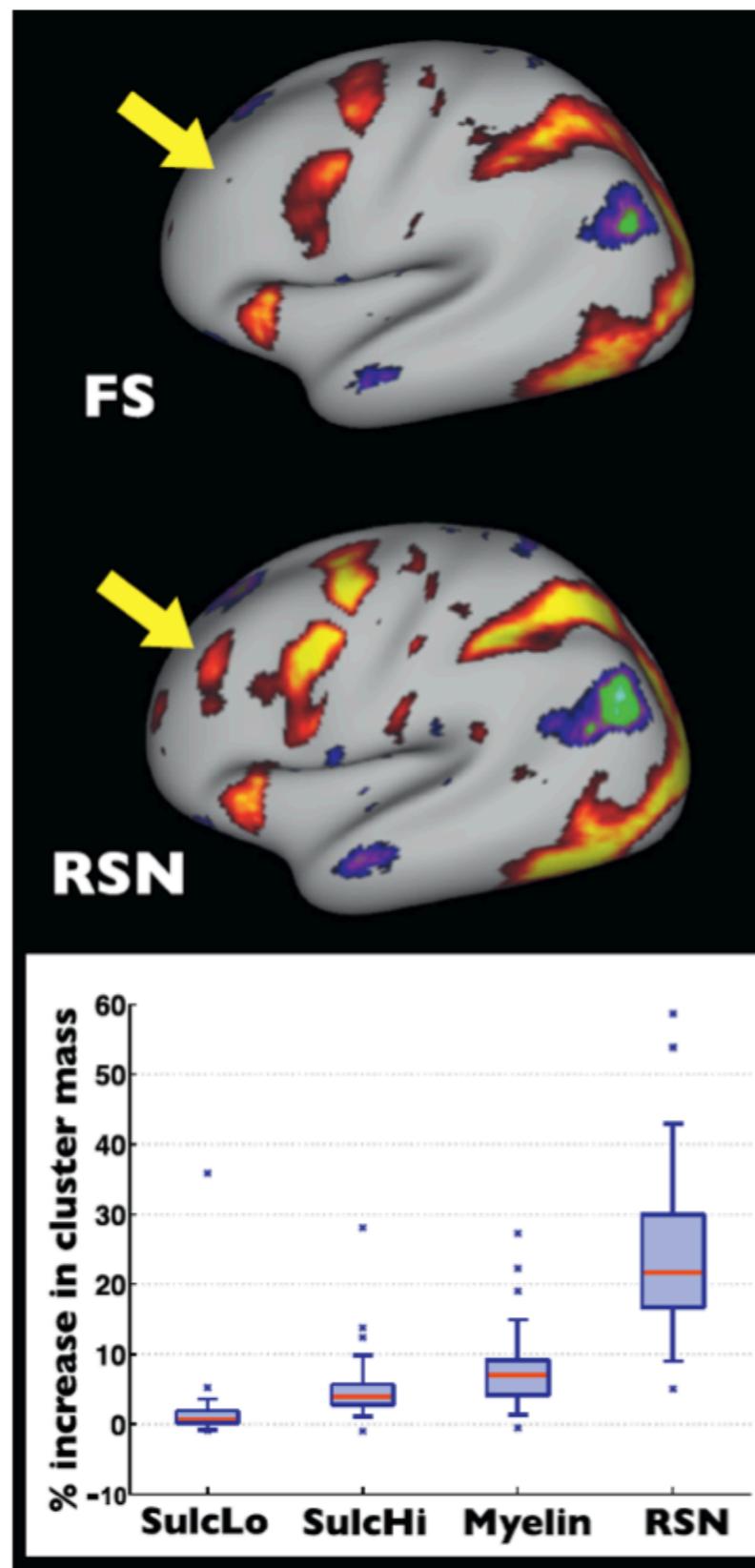
MSM: improves alignment of areal features

- Alignment driven multivariate feature vectors
 - ▶ myelin (M)
 - ▶ rfMRI (R)
 - ▶ visuotopic (V))
- Improves alignment of task activations and correspondence across functional networks

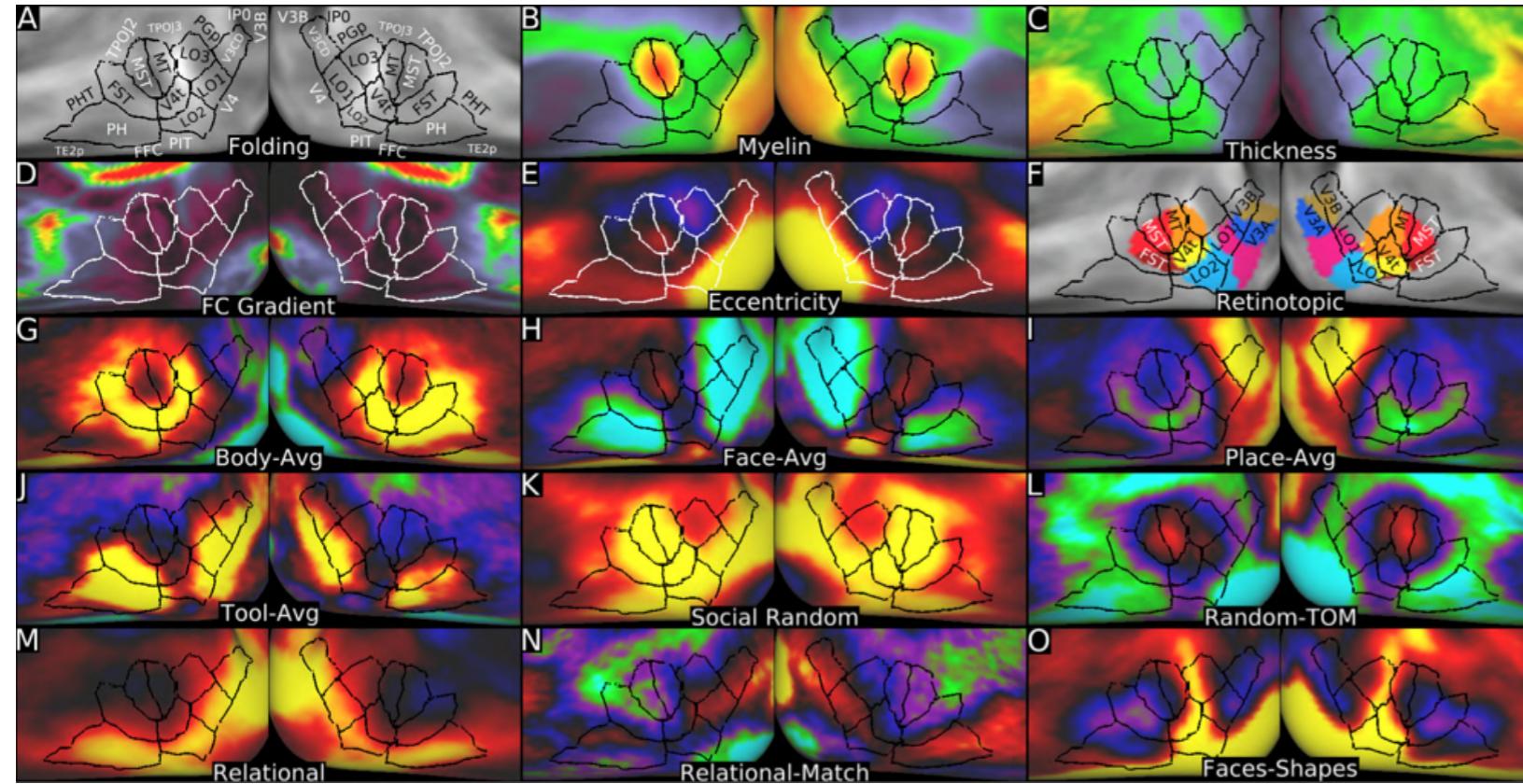


MSM: improves alignment of areal features

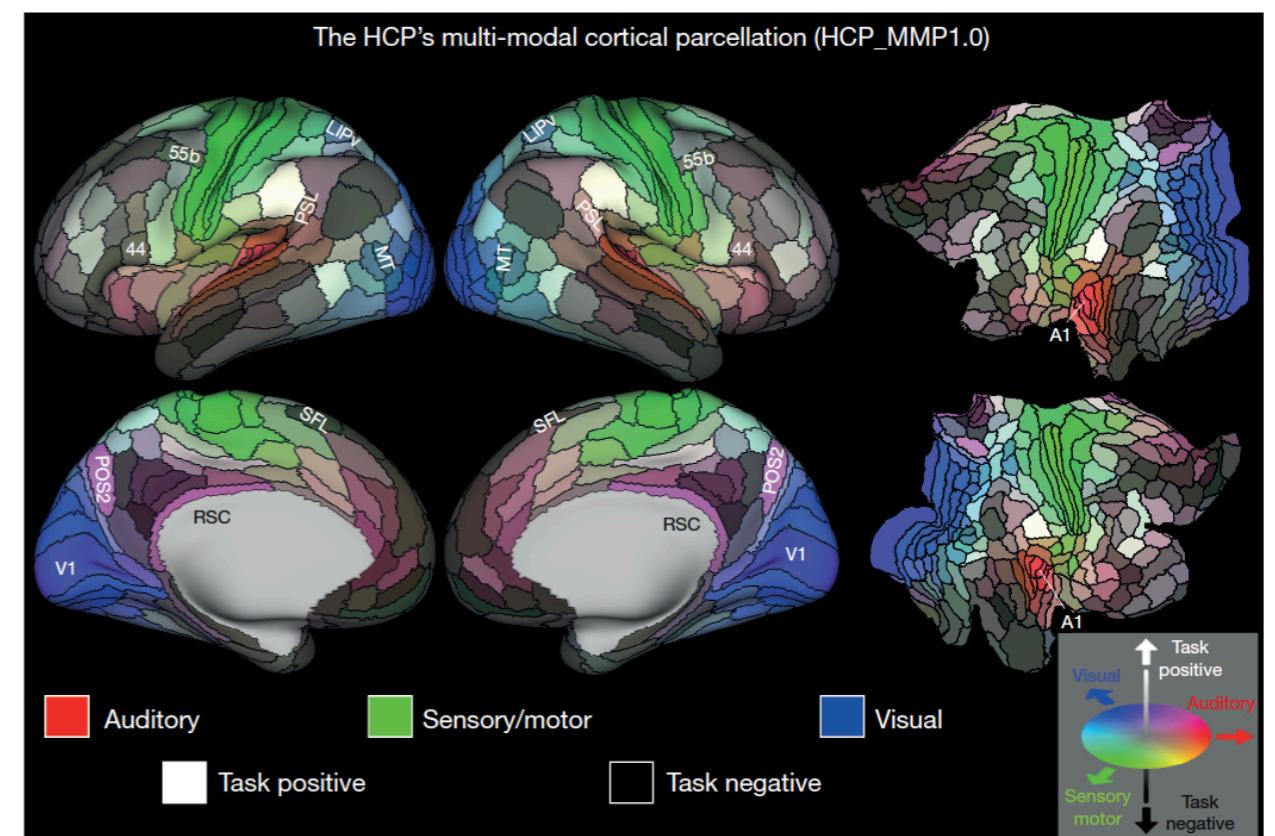
- Alignment driven multivariate feature vectors
 - ▶ myelin (M)
 - ▶ rfMRI (R)
 - ▶ visuotopic (V))
- Improves alignment of task activations and correspondence across functional networks



MSM: HCP Parcellation



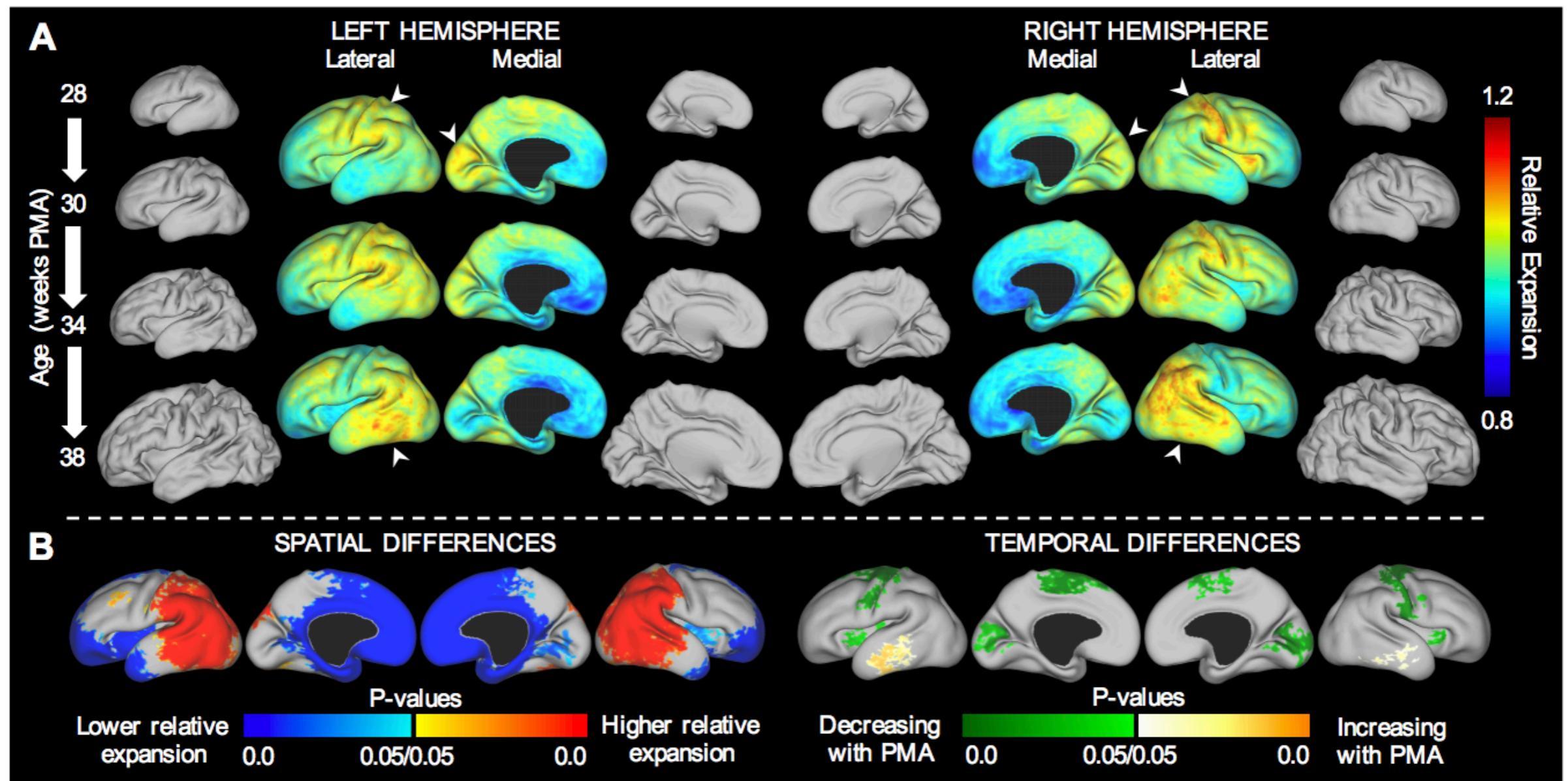
MSM: HCP Parcellation



MSM: finding trends in longitudinal cortical development

- 24 very preterm infants (born <30 weeks PMA, 15 male, 15 female)
- scanned 2-4 times before or at term-equivalent (36-40 weeks PMA)

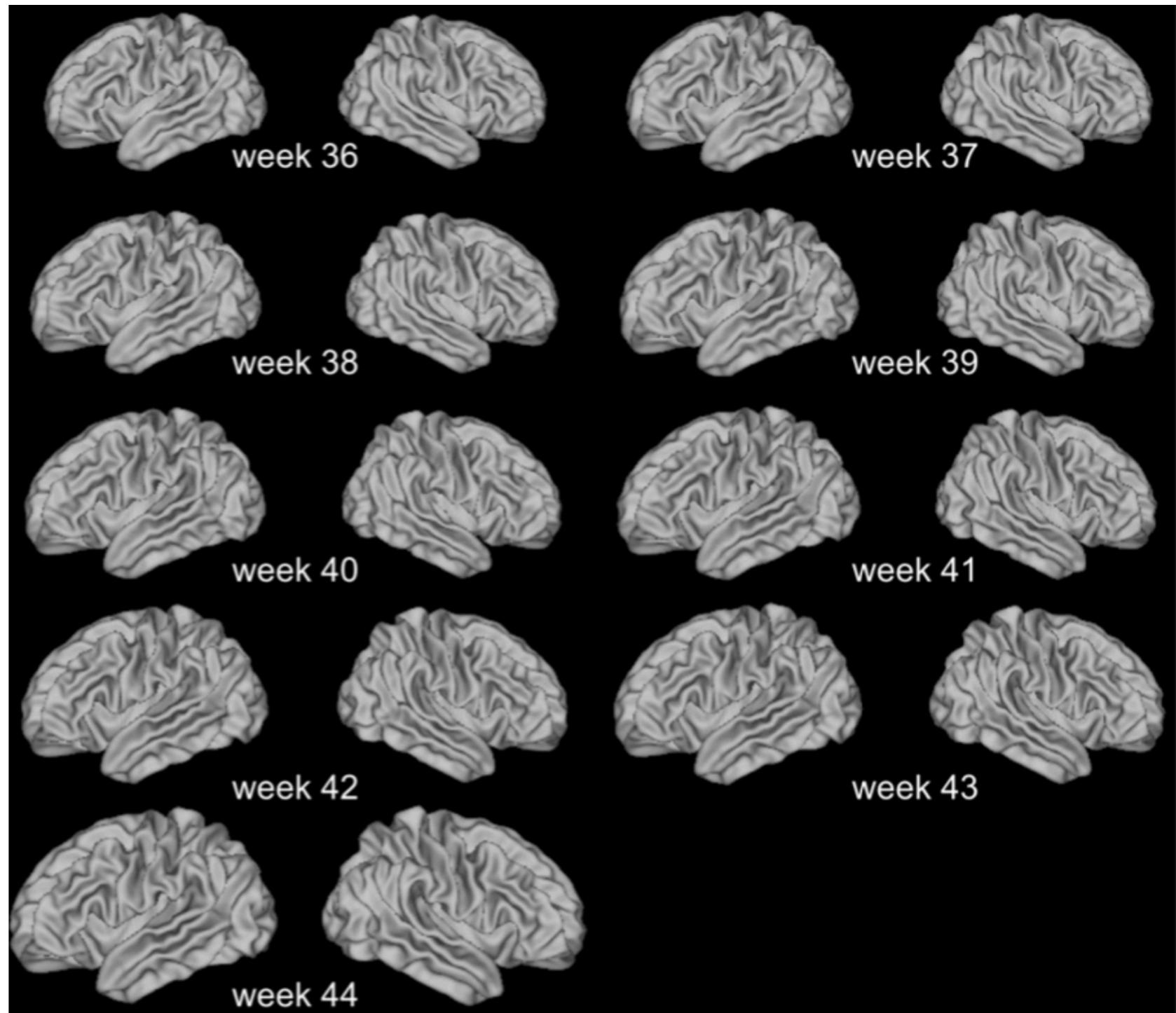
Garcia, Kara E., Robinson E.C. et al. "Dynamic patterns of cortical expansion during folding of the preterm human brain." *PNAS* (2018)



dHCP spatio-temporal atlases

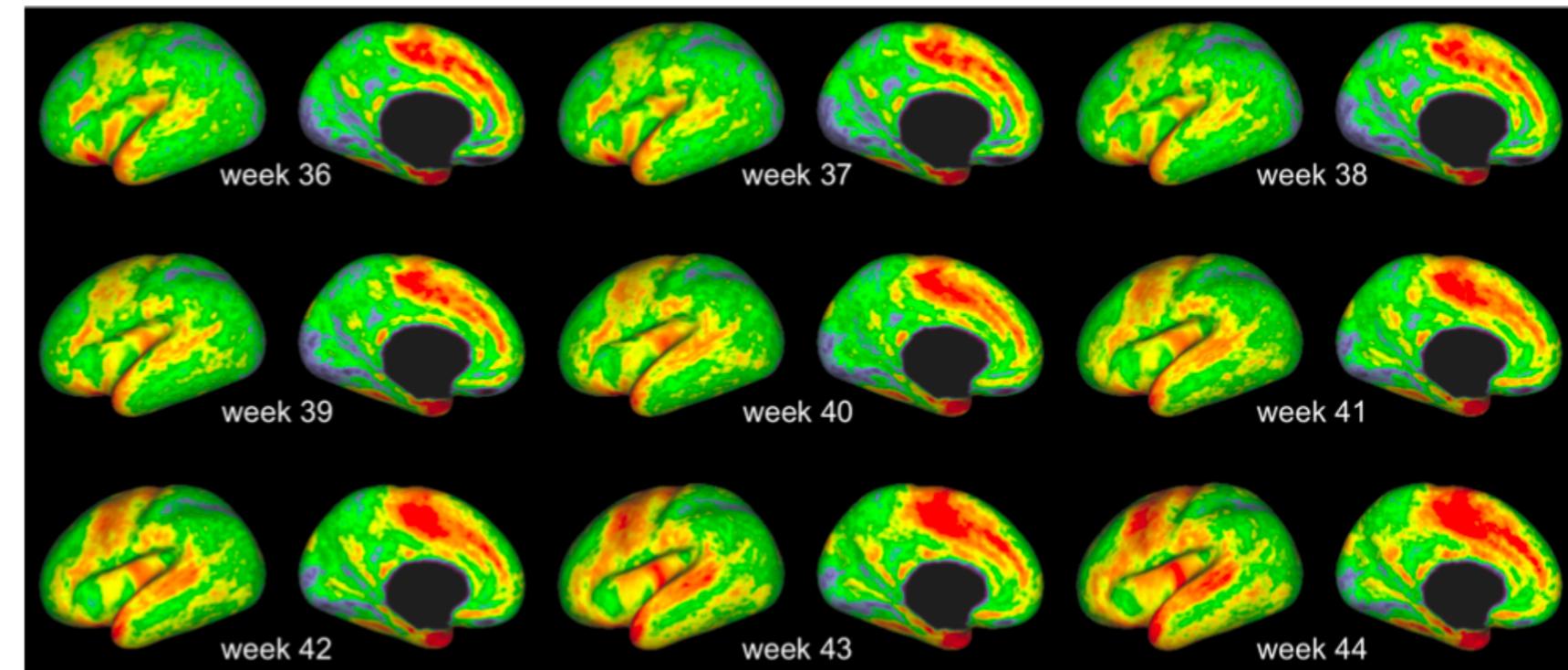
- New volumetric and surface templates spanning 36-44 weeks gestation

Jelena Bozek et al.
Construction of a Neonatal
Cortical Surface Atlas Using
Multimodal Surface
Matching in the Developing
Human Connectome Project
(under revision)



dHCP spatio-temporal atlases

- New volumetric and surface templates spanning 36-44 weeks gestation



Jelena Bozek et al.
Construction of a Neonatal
Cortical Surface Atlas Using
Multimodal Surface
Matching in the Developing
Human Connectome Project

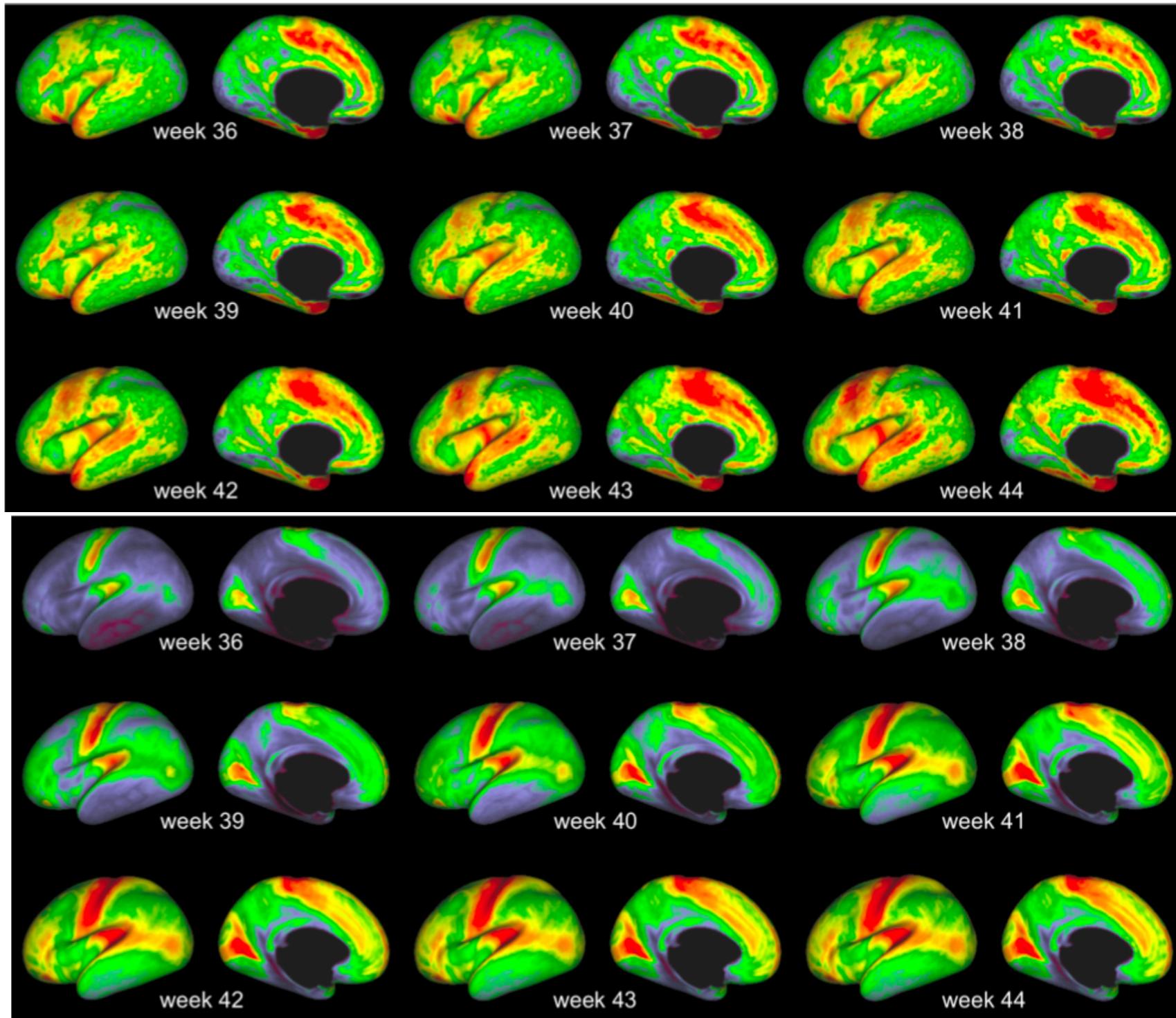
(under revision)

dHCP spatio-temporal atlases

- New volumetric and surface templates spanning 36-44 weeks gestation

Jelena Bozek et al.
Construction of a Neonatal
Cortical Surface Atlas Using
Multimodal Surface
Matching in the Developing
Human Connectome Project

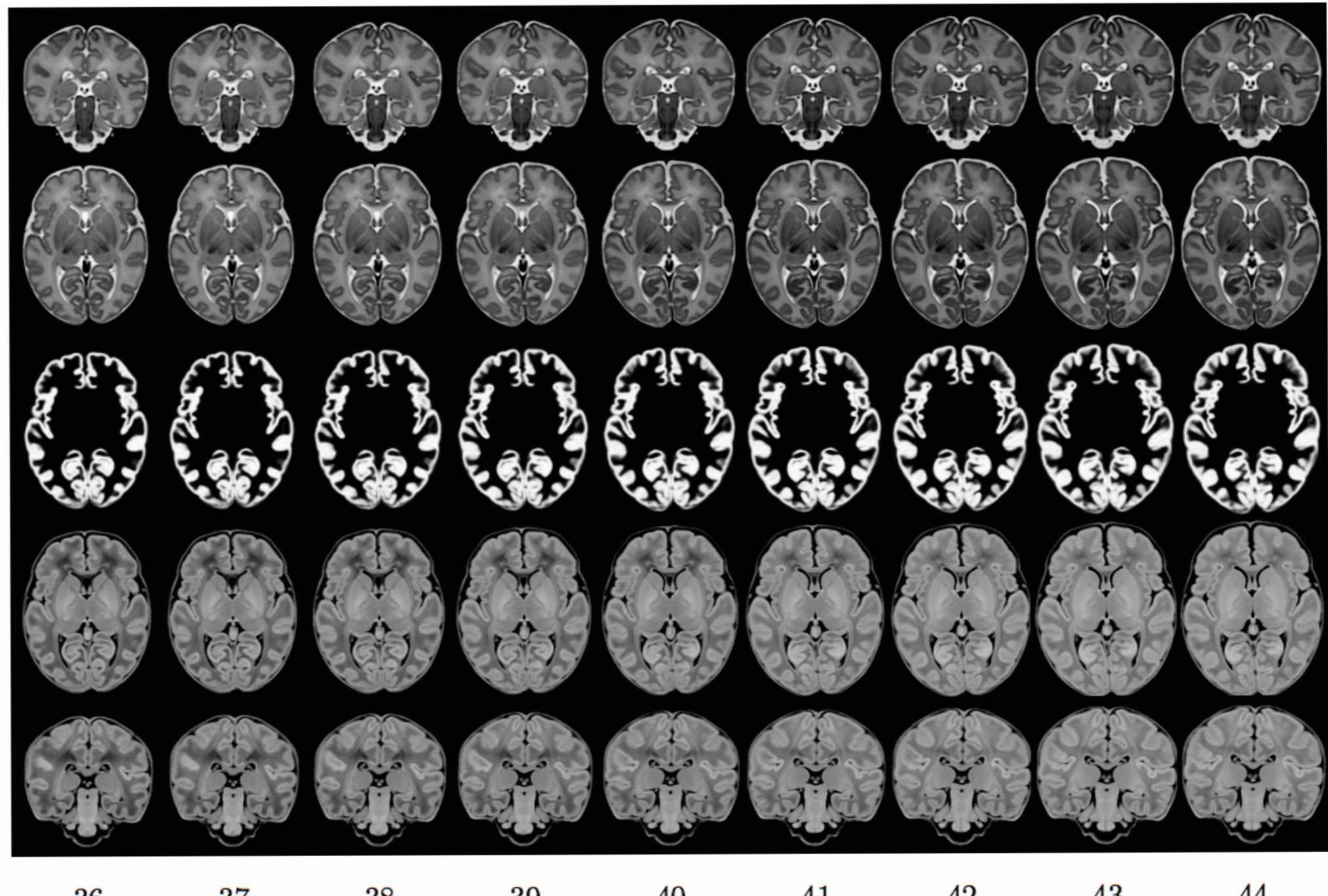
(under revision)



dHCP spatio-temporal atlases

- New volumetric and surface templates spanning 36-44 weeks gestation

Andreas Schuh et al.
*Unbiased construction
of a temporally
consistent
morphological atlas of
neonatal brain
development
(under review)*



Part 2:

- Similarities between dHCP and HCP
- File formats
- fMRI
 - MRI basis
 - Sources of noise
 - Resting state
- Comparisons between HCP and dHCP
 - Functional connectivity
 - rfMRI and behaviour

dHCP Structural Pipeline

- Reconstruction with motion correction

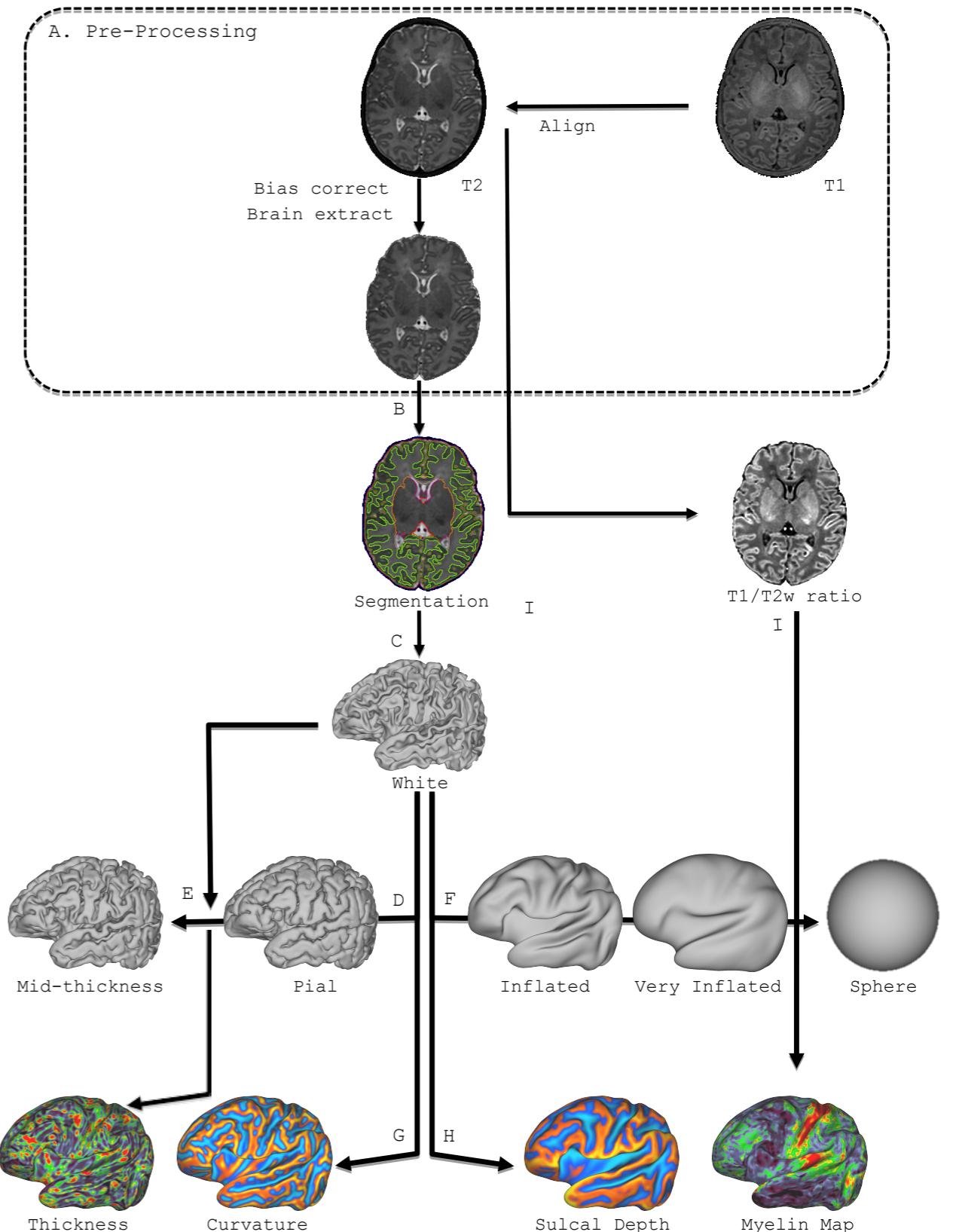
dHCP Structural Pipeline

- Reconstruction with motion correction
- Refined Tissue segmentation
 - New tissue classes for e.g. hypo intense white matter (around ventricles)

Makropoulos, Antonios, et al. "Automatic whole brain MRI segmentation of the developing neonatal brain." *IEEE transactions on medical imaging* 33.9 (2014): 1818-1831.

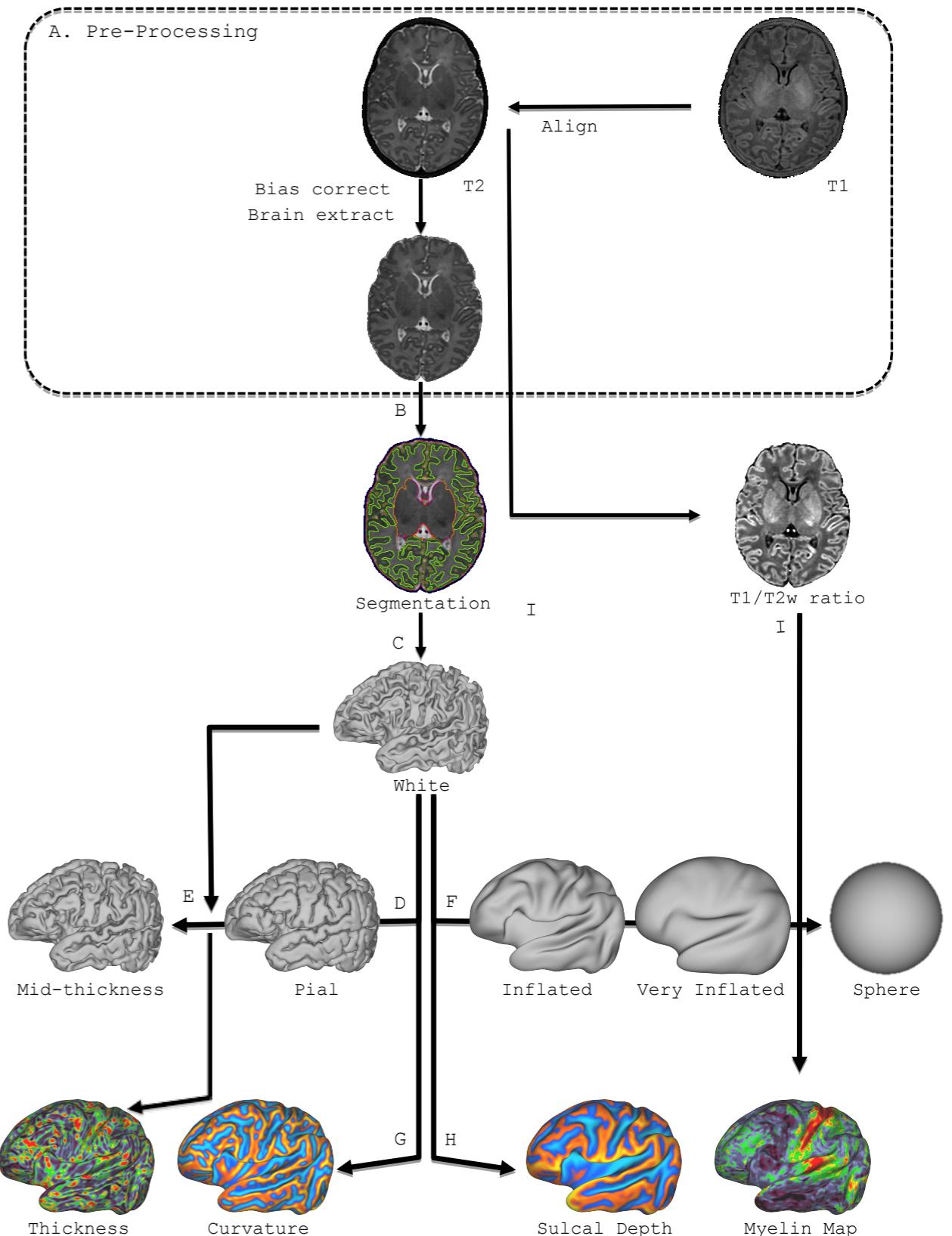
dHCP Structural Pipeline

- Reconstruction with motion correction
- Refined Tissue segmentation
 - New tissue classes for e.g. hypo intense white matter (around ventricles)



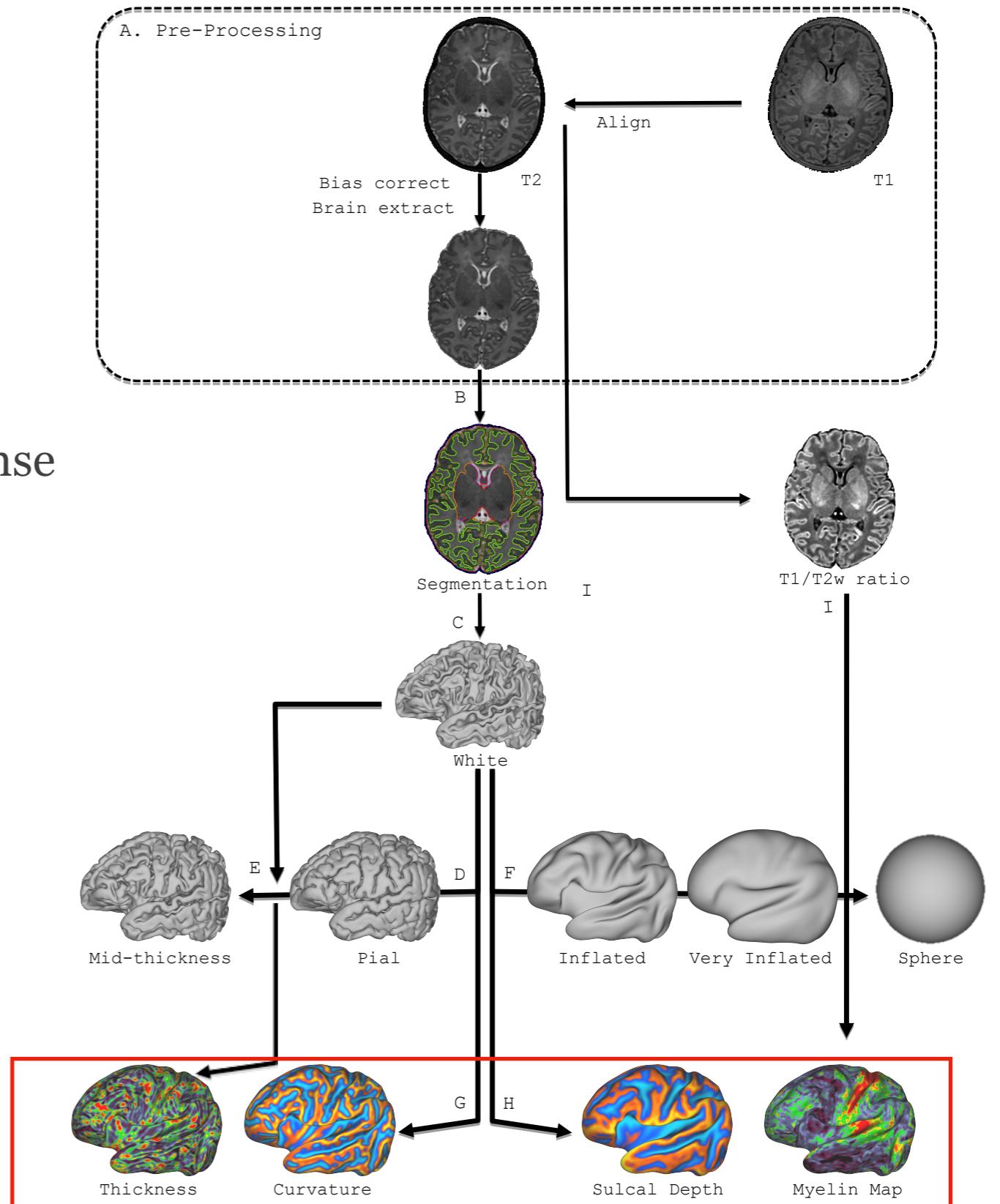
dHCP Structural Pipeline

- Reconstruction with motion correction
- Refined Tissue segmentation
 - New tissue classes for e.g. hypo intense white matter (around ventricles)
- Surface mesh modelling



dHCP Structural Pipeline

- Reconstruction with motion correction
- Refined Tissue segmentation
 - New tissue classes for e.g. hypo intense white matter (around ventricles)
- Surface mesh modelling
- Feature Extraction



HCP and dHCP structural data

Comparison between HCP and dHCP pipelines.sss

	HCP	dHCP
Image Resolution	0.7 mm^3	0.8 mm^3 (0.5 mm^3 after reconstruction)
Total scanning time	4 h	76 min
Preprocessing		
Gradient Distortion Correction	Yes	No
Read-out distortion correction	Yes	No
Brain Extraction	Propagation of atlas mask	BET
T1 - T2 registration	BBR	Rigid Alignment, BBR
Bias Correction	$\sqrt{T1*T2}$	N4
Segmentation/Surface extraction		
Performed on	T1	T2
Tissue Segmentation	FreeSurfer	Draw-EM
White and Pial Surface Extraction	Modified FreeSurfer	Schuh et al. (2017)
Surface Inflation	FreeSurfer	FreeSurfer re-implementation
Spherical Projection	FreeSurfer	spherical MDS
Myelin Mapping	T1/T2	T1/T2

- Structural pipelines are very similar with exception to segmentation protocol

Comparing dHCP and HCP morphological features

Comparing dHCP and HCP morphological features

- See wb_view

Comparing dHCP and HCP morphological features

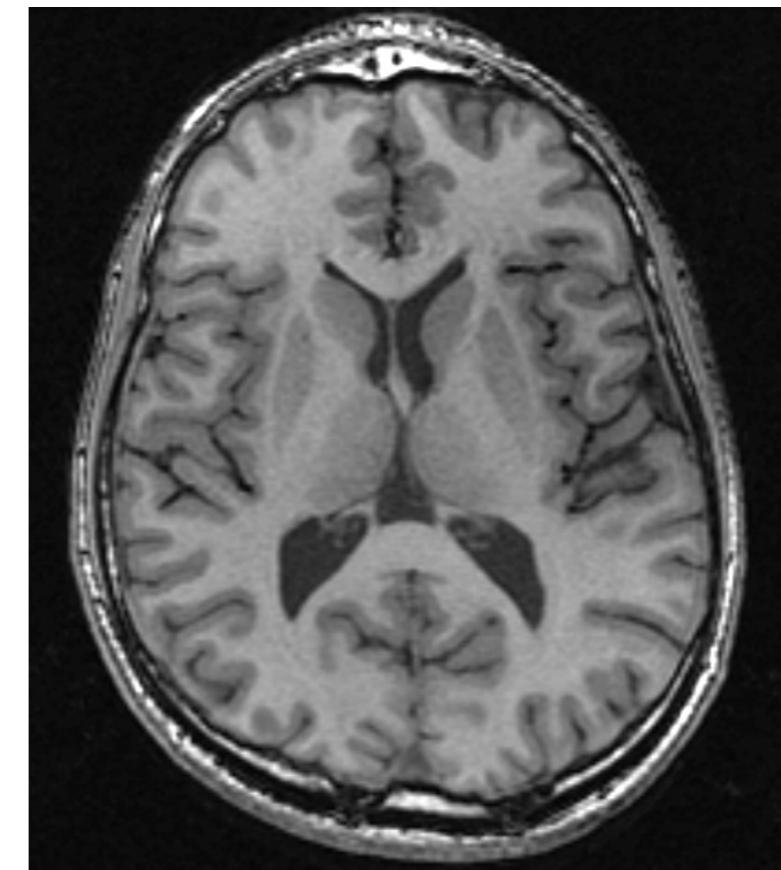
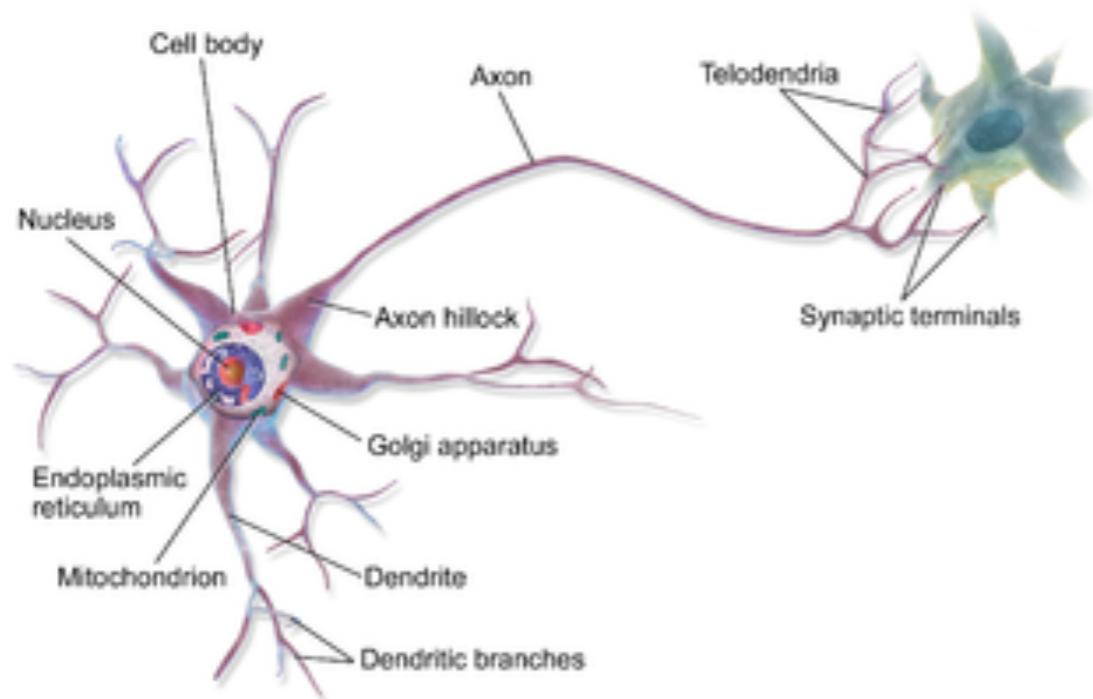
- See wb_view
- Very similar

Comparing dHCP and HCP morphological features

- See wb_view
- Very similar
- Completely not the case for fMRI and dMRI
 - ▶ More mature microstructure
 - ▶ Each HCP dMRI and fMRI scan is > 1hr (longer than the entire dHCP scan time)

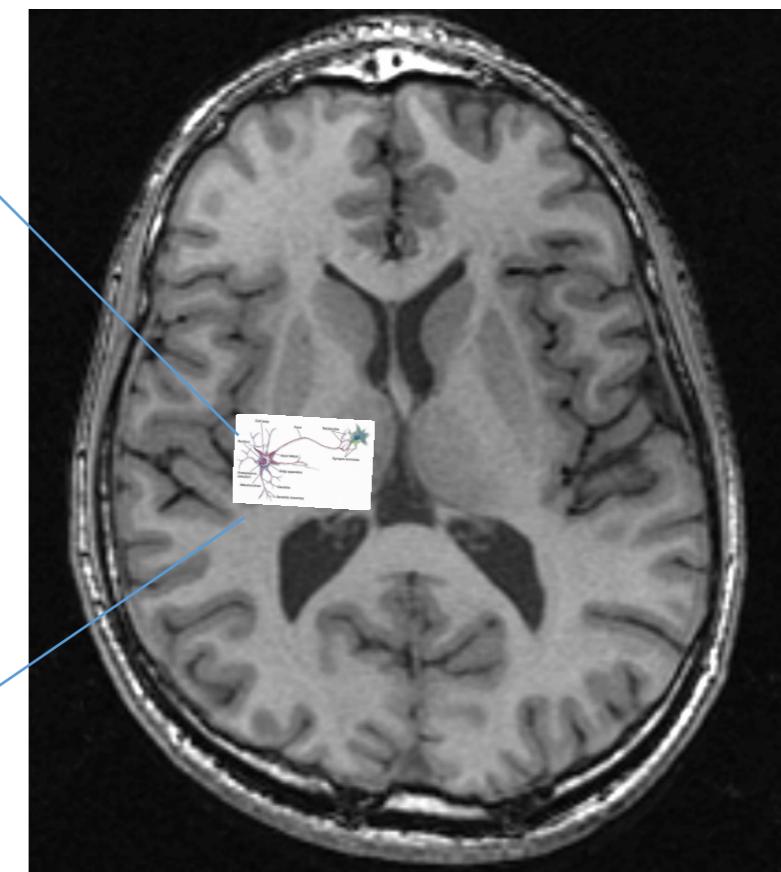
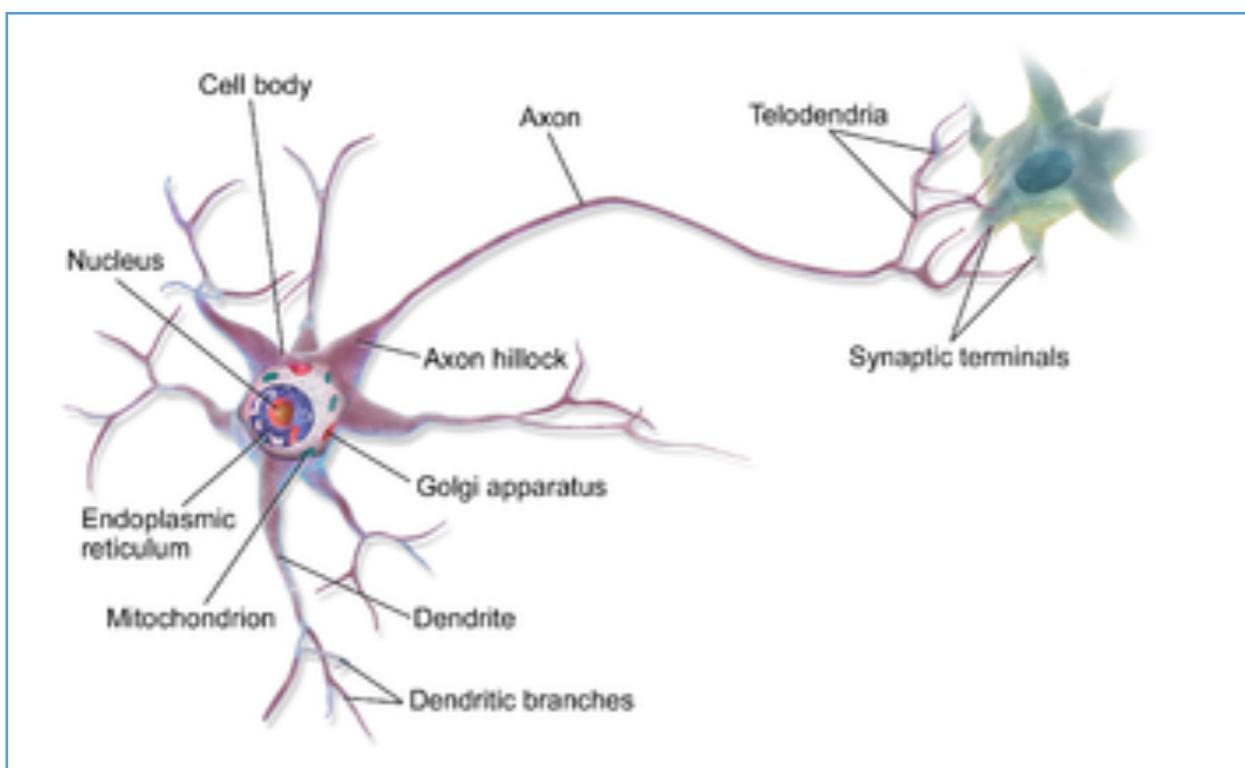
fMRI

What is brain function?



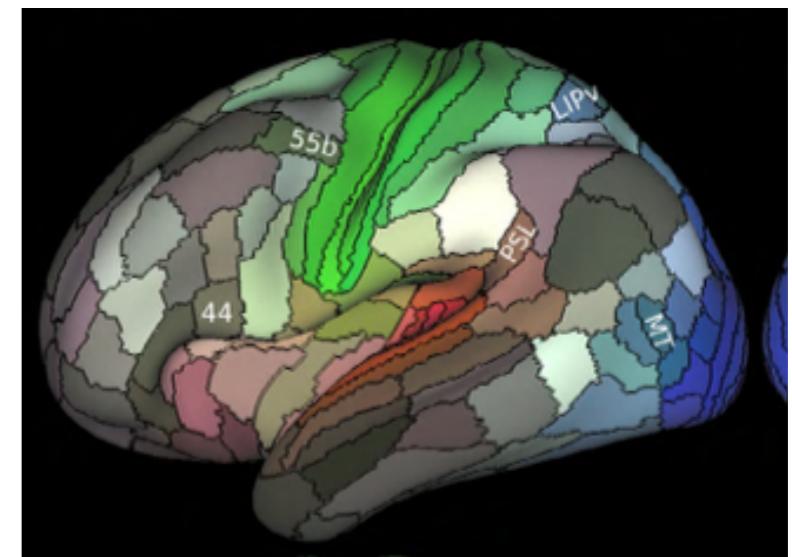
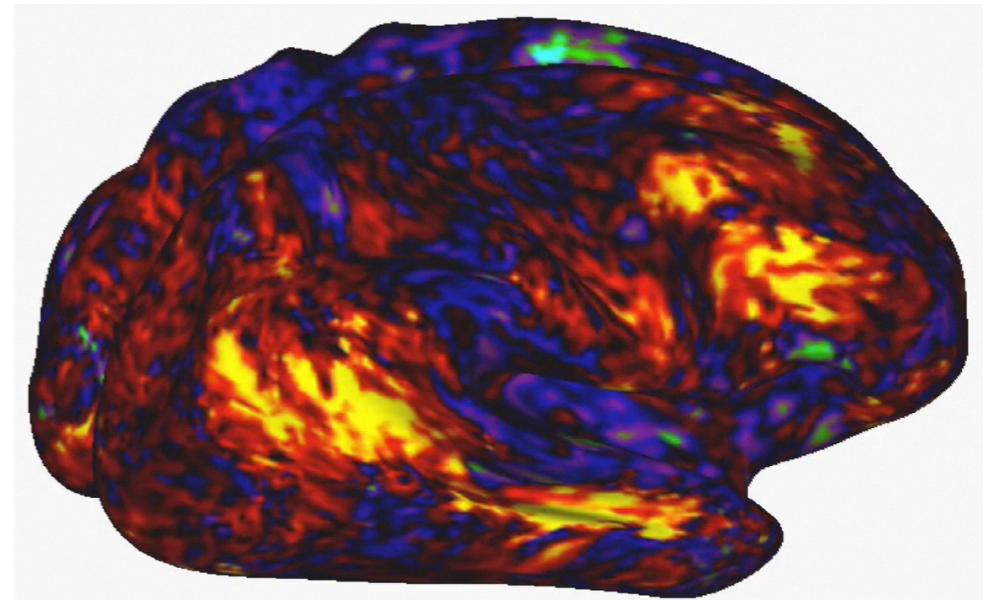
fMRI

What is brain function?

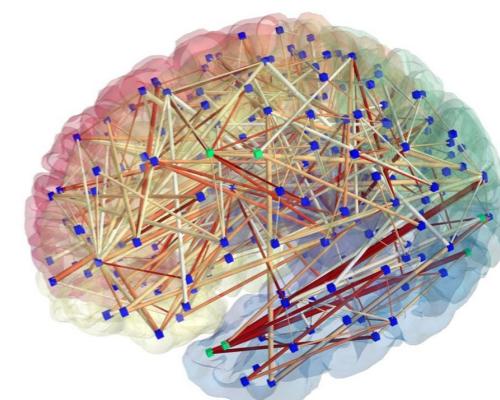


fMRI

- ‘What Wires Together Fires together’
- Patterns of coordinated activity
- Regions of the brain with functional specialisation
- Connected in a network

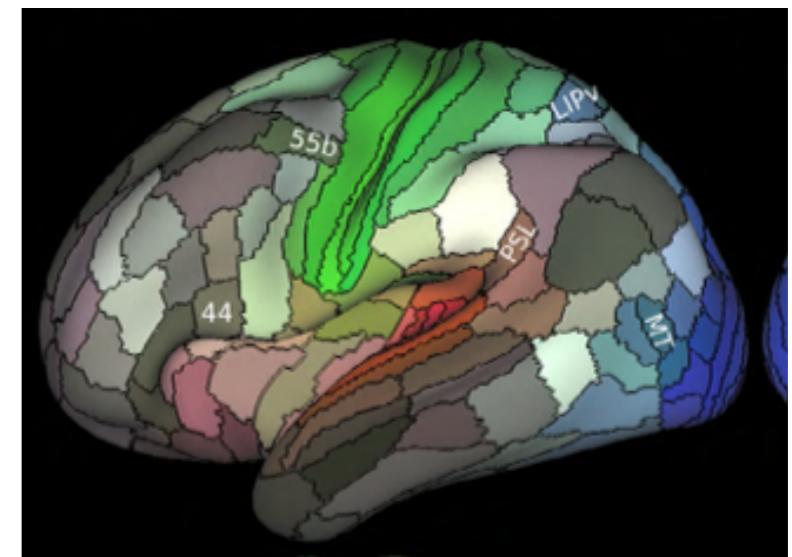
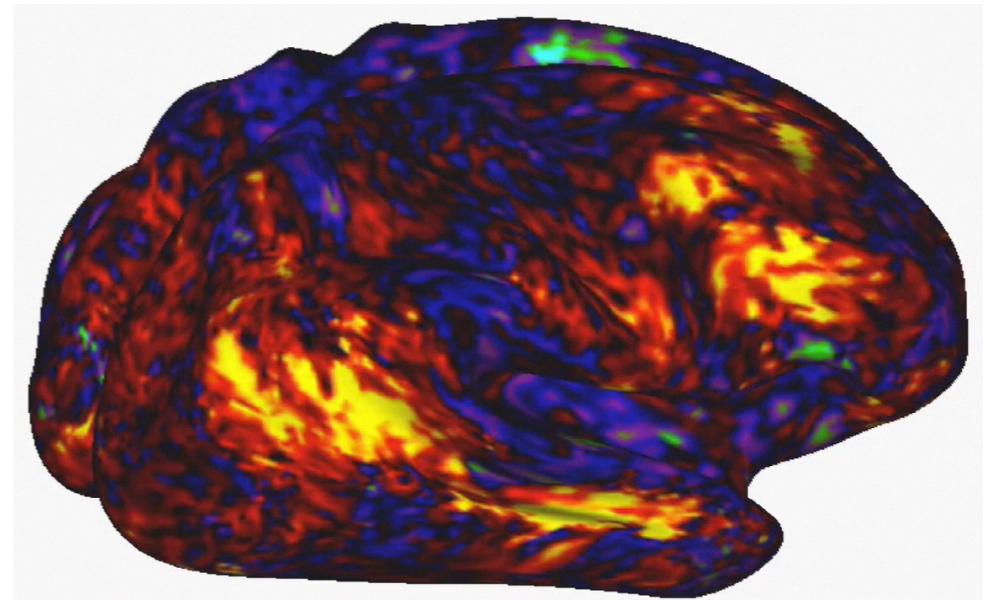


c/o The WU-MINN Human Connectome Project (Nature)

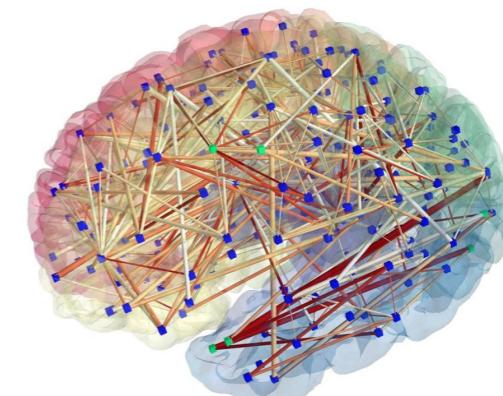


fMRI

- ‘What Wires Together Fires together’
- Patterns of coordinated activity
- Regions of the brain with functional specialisation
- Connected in a network

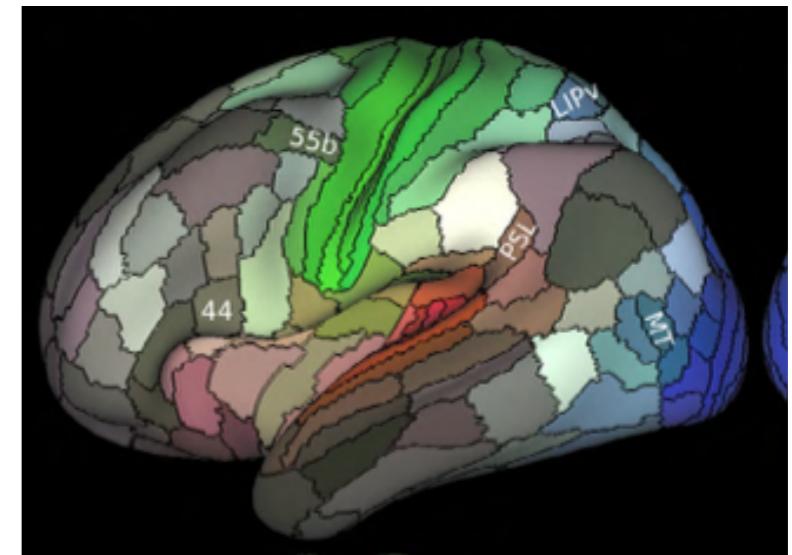
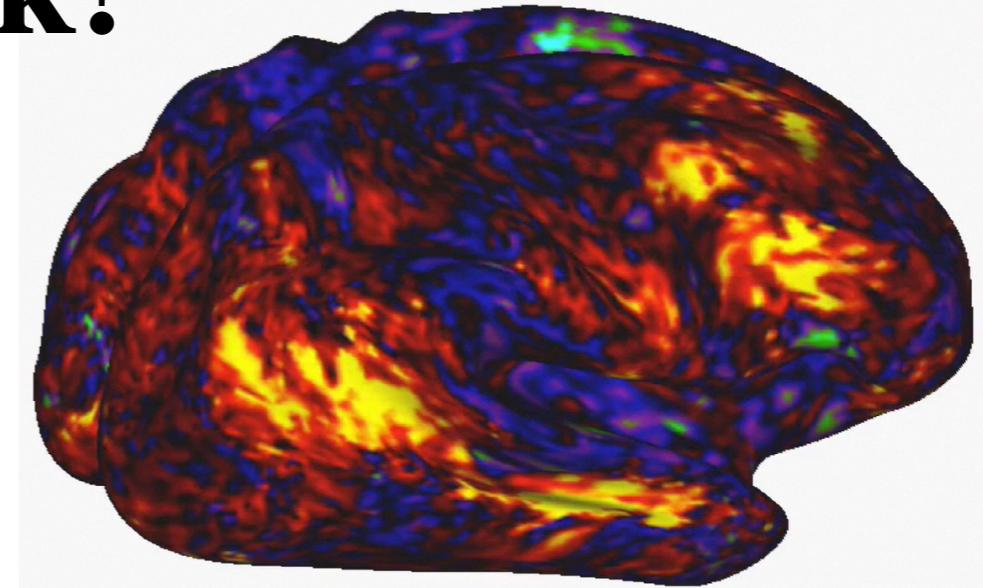


c/o The WU-MINN Human Connectome Project (Nature)

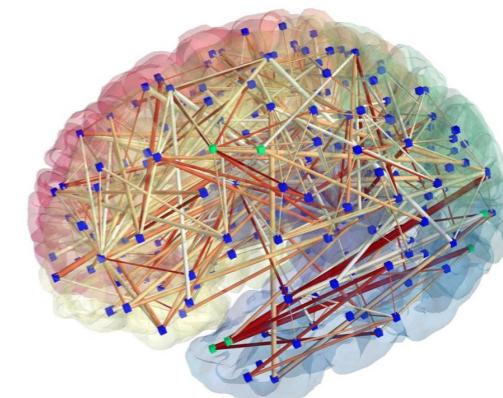


fMRI: how does it work?

- Brain activity is electrical signalling:
- Requires energy - supplied from oxygen and glucose
- Nutrients are supplied from the blood (cells have no energy store)

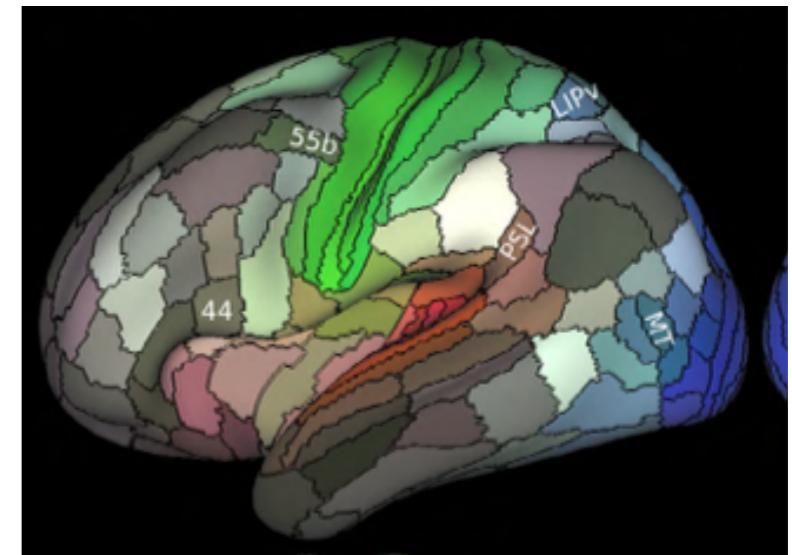
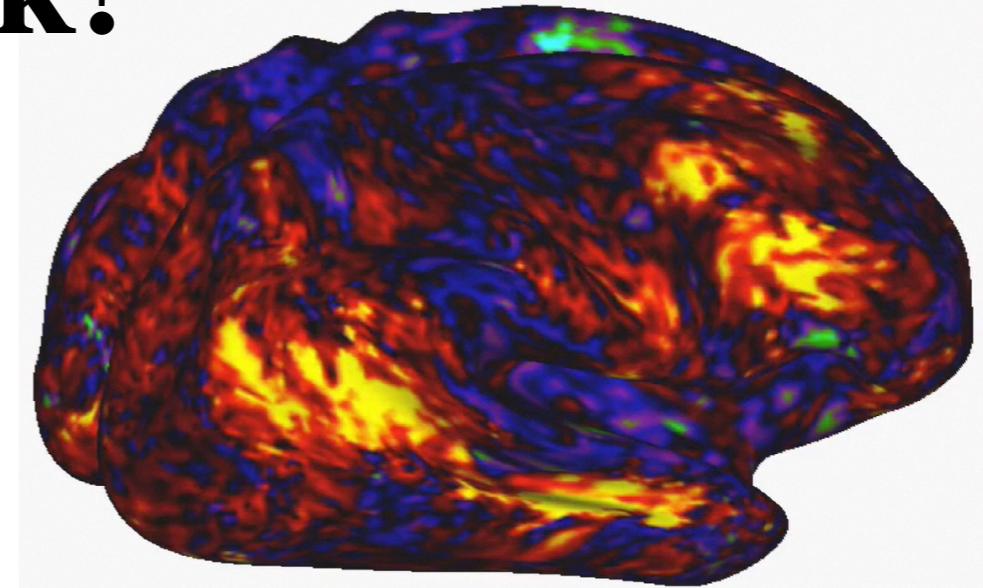


c/o The WU-MINN Human Connectome Project (Nature)

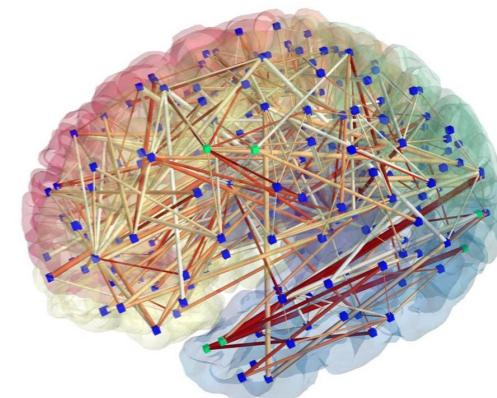


fMRI: how does it work?

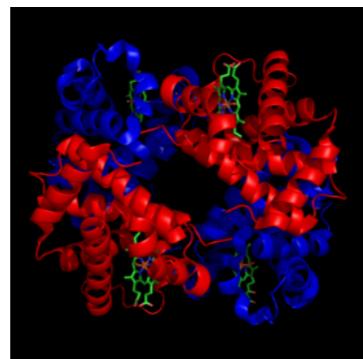
- Brain activity is electrical signalling:
- Requires energy - supplied from oxygen and glucose
- Nutrients are supplied from the blood (cells have no energy store)



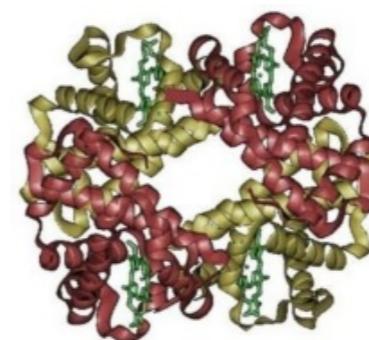
c/o The WU-MINN Human Connectome Project (Nature)



Haemodynamic Response



Deoxyhaemoglobin:
paramagnetic
(weakly attracted)

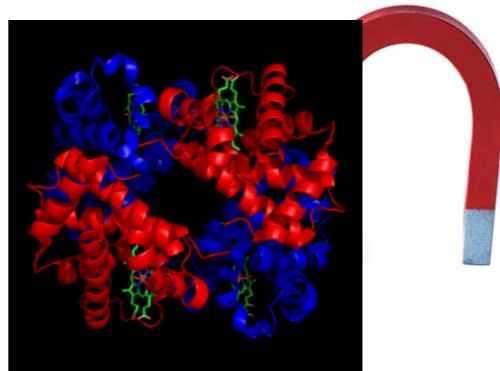


Oxyhaemoglobin:
diamagnetic
(repelled)

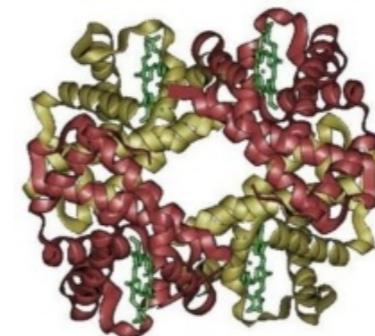
Therefore deoxy-Hb leads to

- local magnetic field inhomogeneity ...
- Dephasing of Hydrogen proton spins
- More rapid T₂* decay
- and a *decrease* in **BOLD** signal

Haemodynamic Response



Deoxyhaemoglobin:
paramagnetic
(weakly attracted)

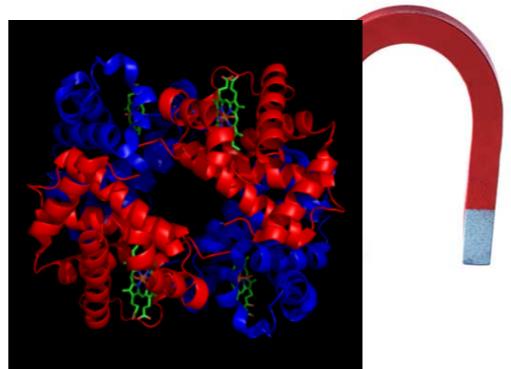


Oxyhaemoglobin:
diamagnetic
(repelled)

Therefore deoxy-Hb leads to

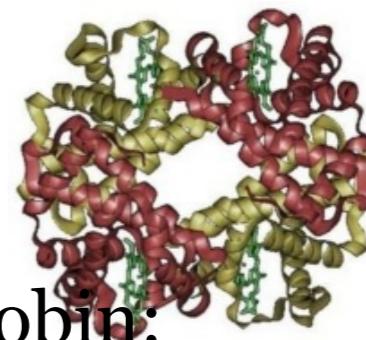
- local magnetic field inhomogeneity ...
- Dephasing of Hydrogen proton spins
- More rapid T_{2^*} decay
- and a *decrease* in **BOLD** signal

Haemodynamic Response



Deoxyhaemoglobin:
paramagnetic
(weakly attracted)

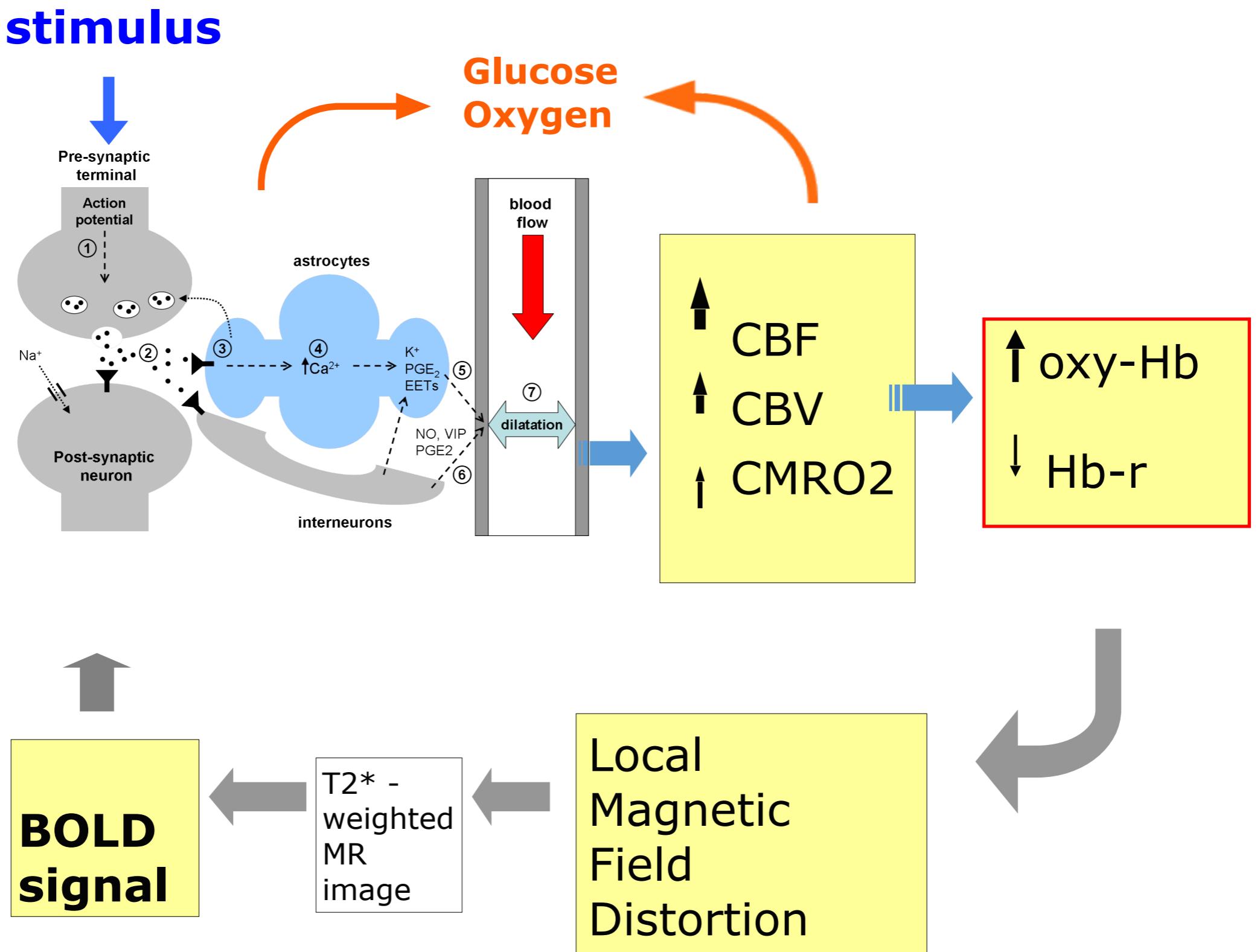
Oxyhaemoglobin:
diamagnetic
(repelled)



Therefore deoxy-Hb leads to

- local magnetic field inhomogeneity ...
- Dephasing of Hydrogen proton spins
- More rapid T₂* decay
- and a *decrease* in **BOLD** signal

fMRI: Indirect measure of neural activity



fMRI: Indirect measure of neural activity

Paradoxically...

Increase in neuronal activity

- increase in venous blood oxygenation*
- *positive BOLD signal.*

*(and an associated decrease in paramagnetic deoxyhemoglobin)

This is due to the fact that the fractional increase in cerebral blood flow (CBF) is larger than the increase in the cerebral metabolic rate of oxygen consumption (CMRO₂),

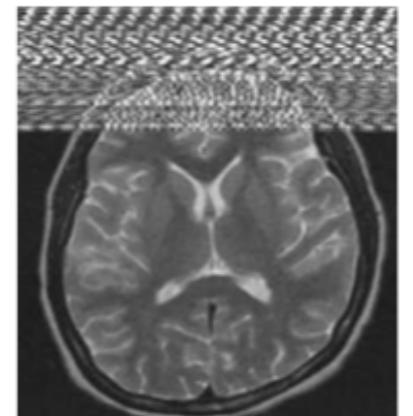
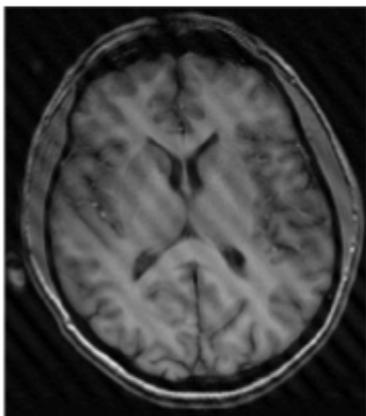
- Scanner Artifacts
- Head Motion
- Physiological e.g. cardiac and respiratory

Many sources of noise....

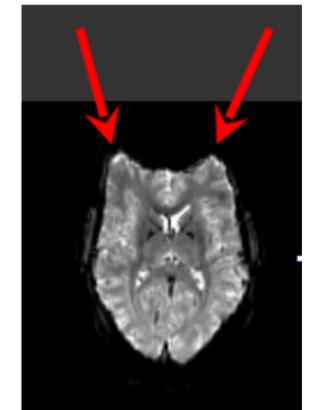
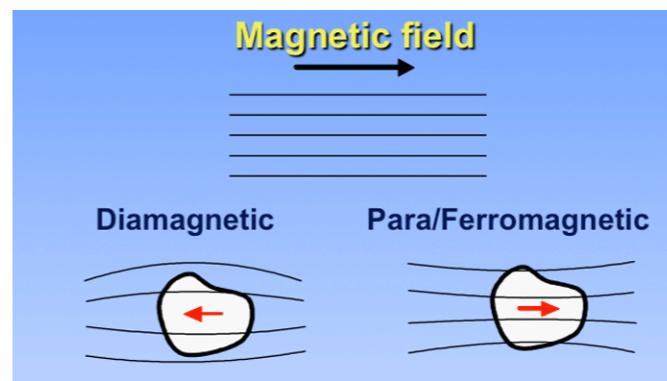
Scanner Artifacts:

- Hardware issues:
 - RF spikes/interference
- Thermal noise
 - Movement of charged particles
- Susceptibility artifacts
 - Diamagnetic materials (bone/tissue) respond differently to paramagnetic materials (air pockets) in magnetic field
 - Impacts spatial (phase encoding) encoding

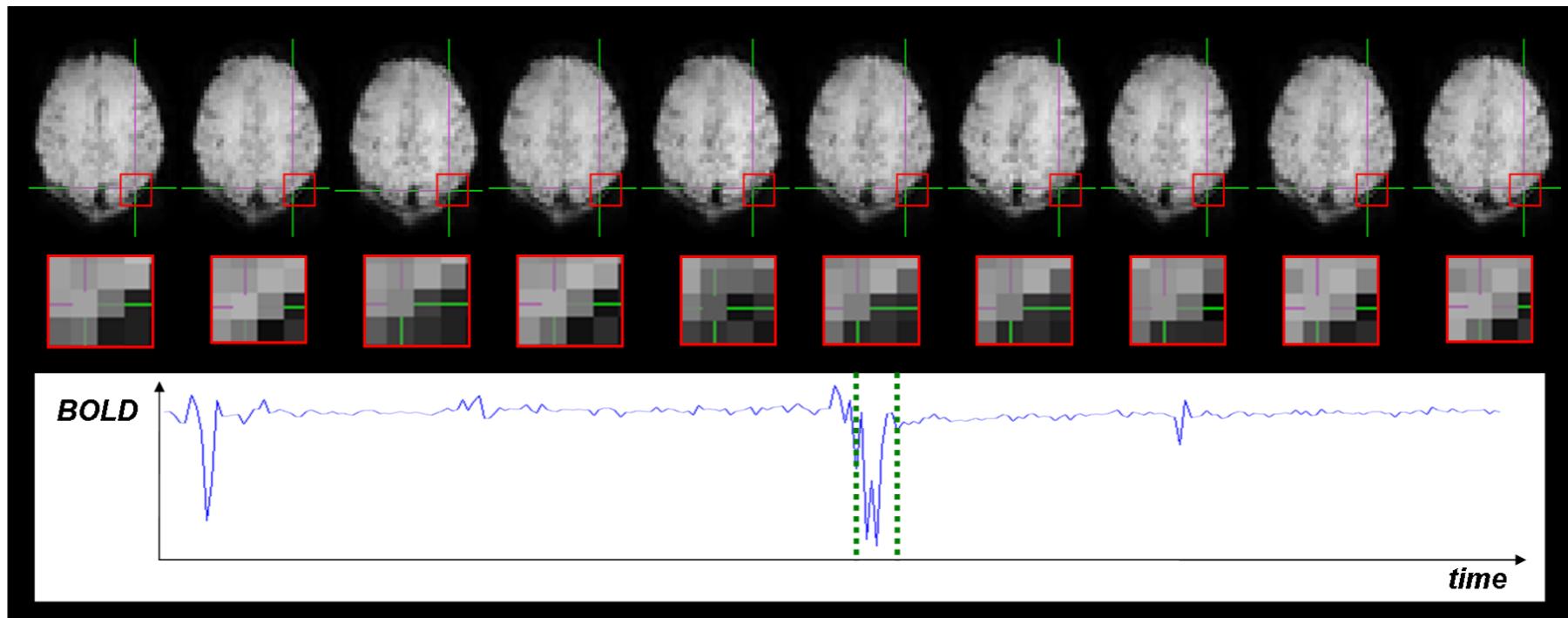
RF interference



Susceptibility



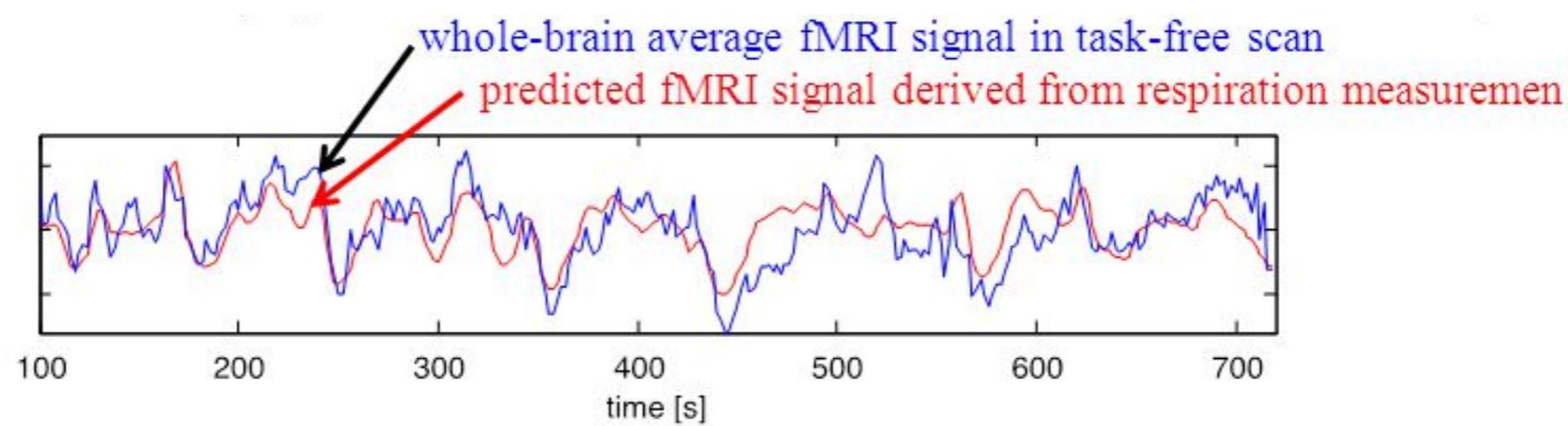
Motion correction



- Even a small movement can cause a significant change in the BOLD signal

Physiological noise:

- e.g. Cardiac, Respiration
- Impact blood flow across the brain



fMRI clean-up

fMRI clean-up

- Spatial filtering?

fMRI clean-up

- Spatial filtering?
 - Field map correction
- } Address scanner artifacts

fMRI clean-up

- Spatial filtering?
 - Field map correction
 - Head motion correction
- } Address scanner artifacts

fMRI clean-up

- Spatial filtering?
 - Field map correction
 - Head motion correction
 - Highpass / lowpass temporal filters
- } Address scanner artifacts

fMRI clean-up

- Spatial filtering?
 - Field map correction
 - Head motion correction
 - Highpass / lowpass temporal filters
 - Estimate “confound” timeseries & regress these out of the data e.g. using learning based methods (FIX)
- 
- } Address scanner artifacts

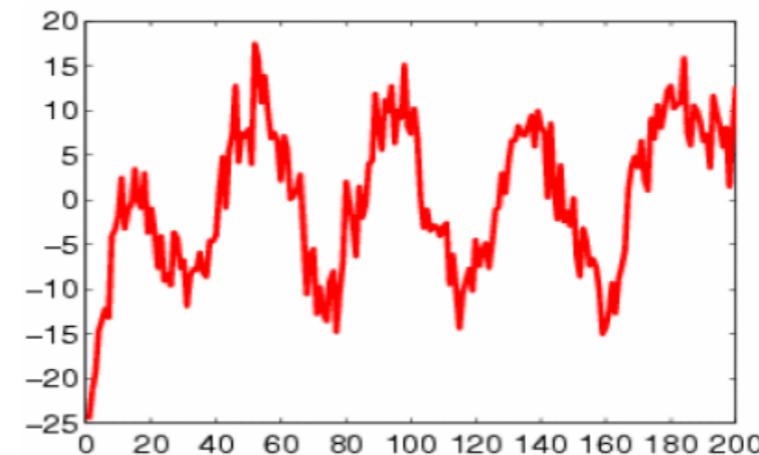
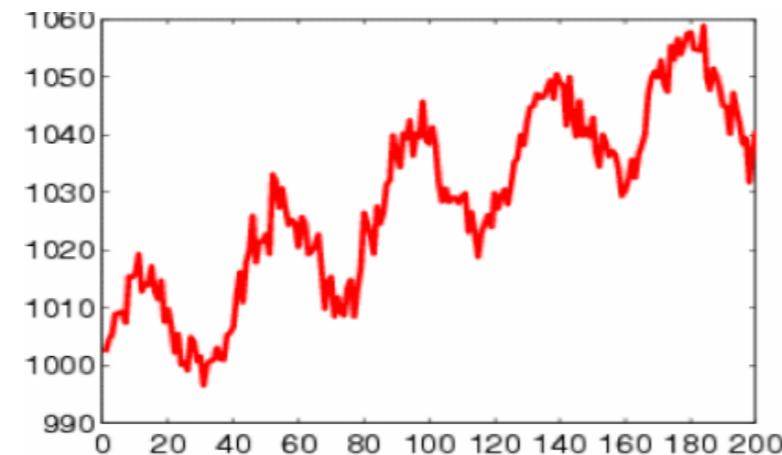
Temporal filtering

Highpass temporal filtering (e.g., remove $f < 0.001$ Hz)

- Reasonable to remove slowest data drifts

Lowpass temporal filtering (e.g., common to remove $f > 0.1$ Hz) - Noise?

- **May remove useful signal**
- Not guaranteed to remove much artefact



High pass

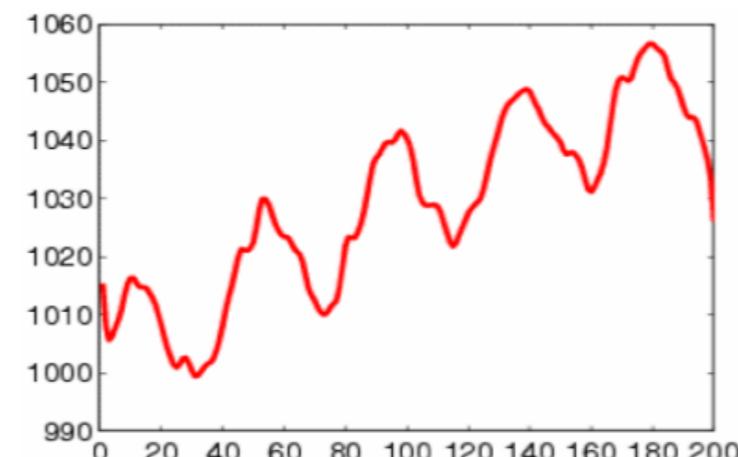
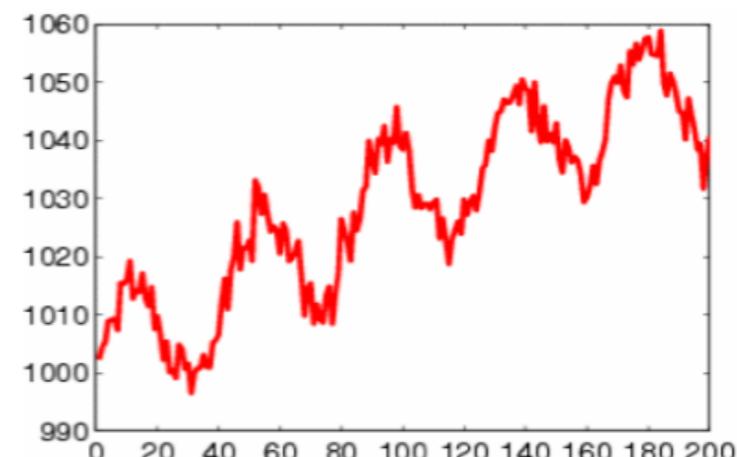
Temporal filtering

Highpass temporal filtering (e.g., remove $f < 0.001$ Hz)

- Reasonable to remove slowest data drifts

Lowpass temporal filtering (e.g., common to remove $f > 0.1$ Hz) - Noise?

- **May remove useful signal**
- Not guaranteed to remove much artefact



Low pass

Temporal filtering

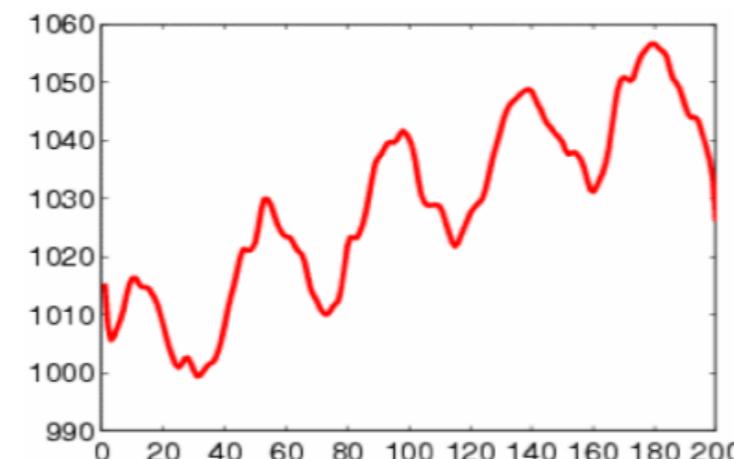
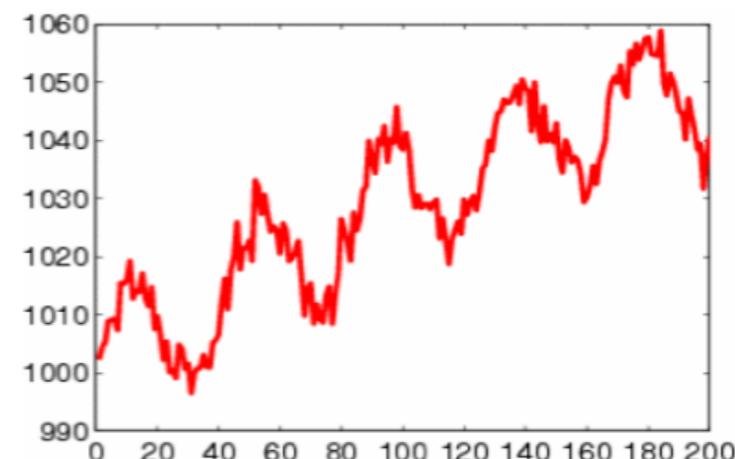
Highpass temporal filtering (e.g., remove $f < 0.001$ Hz)

- Reasonable to remove slowest data drifts



Lowpass temporal filtering (e.g., common to remove $f > 0.1$ Hz) - Noise?

- **May remove useful signal**
- Not guaranteed to remove much artefact



Low pass

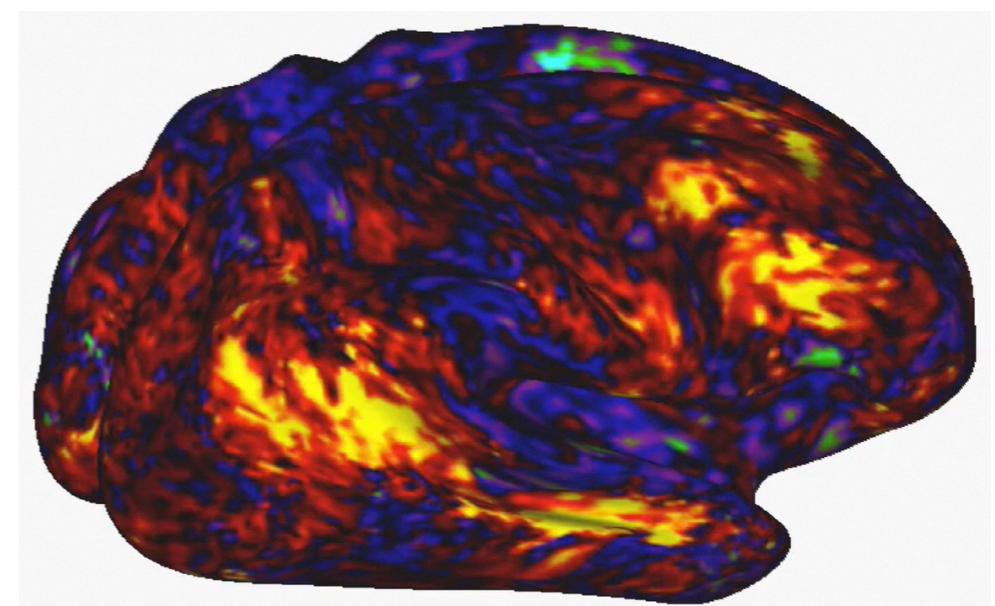
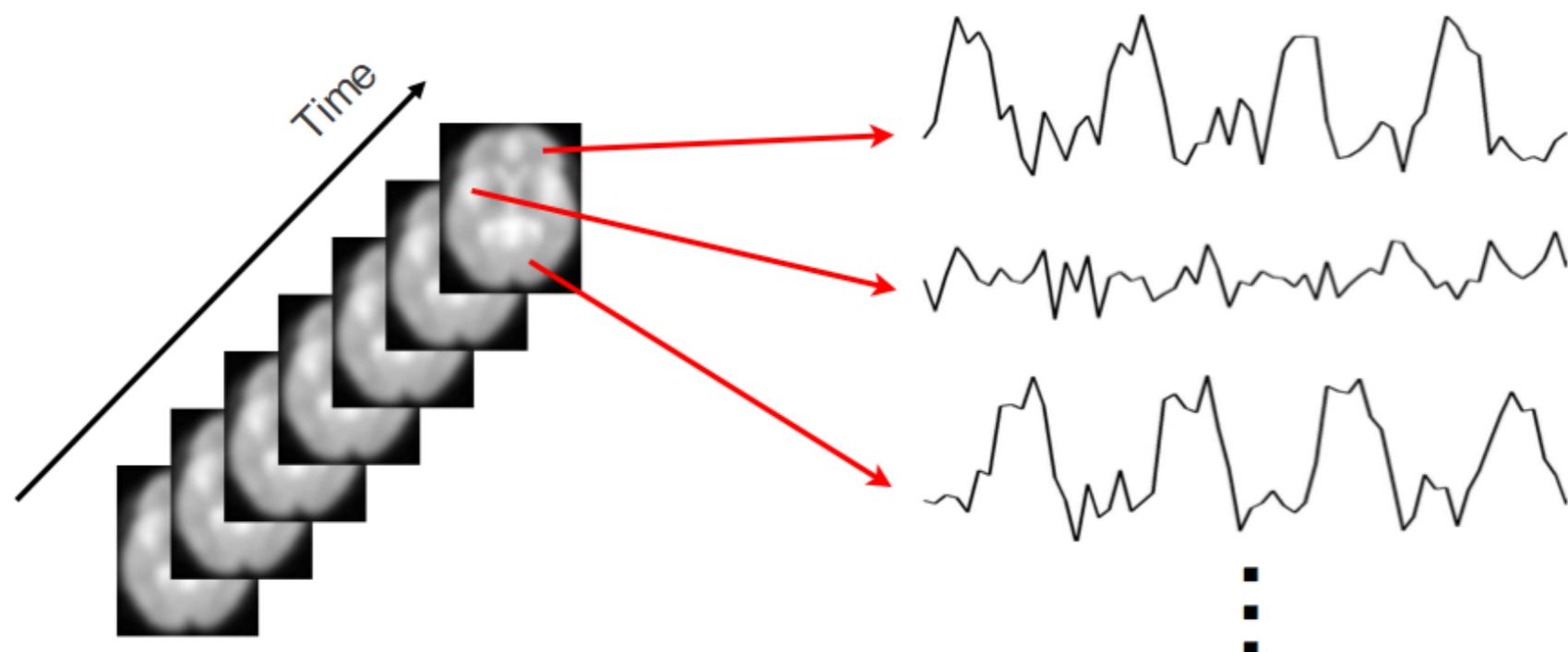
fMRI paradigms

- Task-based fMRI
 - Can we identify which parts of the brain are active (co-active)
 - When performing different tasks
 - Requires stimuli
- Resting State fMRI
 - What does the brain do when it is 'doing nothing'?
 - No stimulus needed

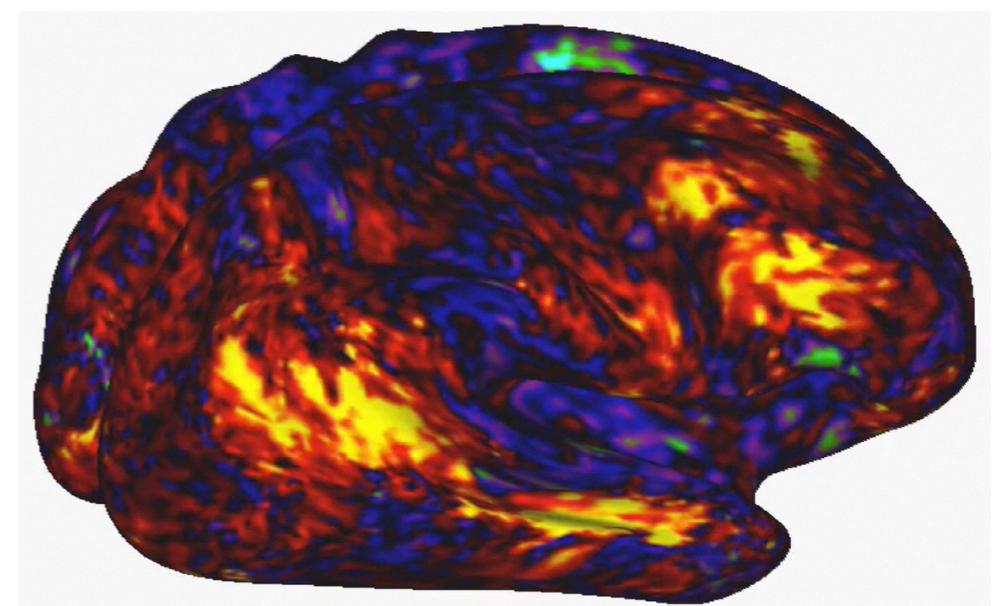
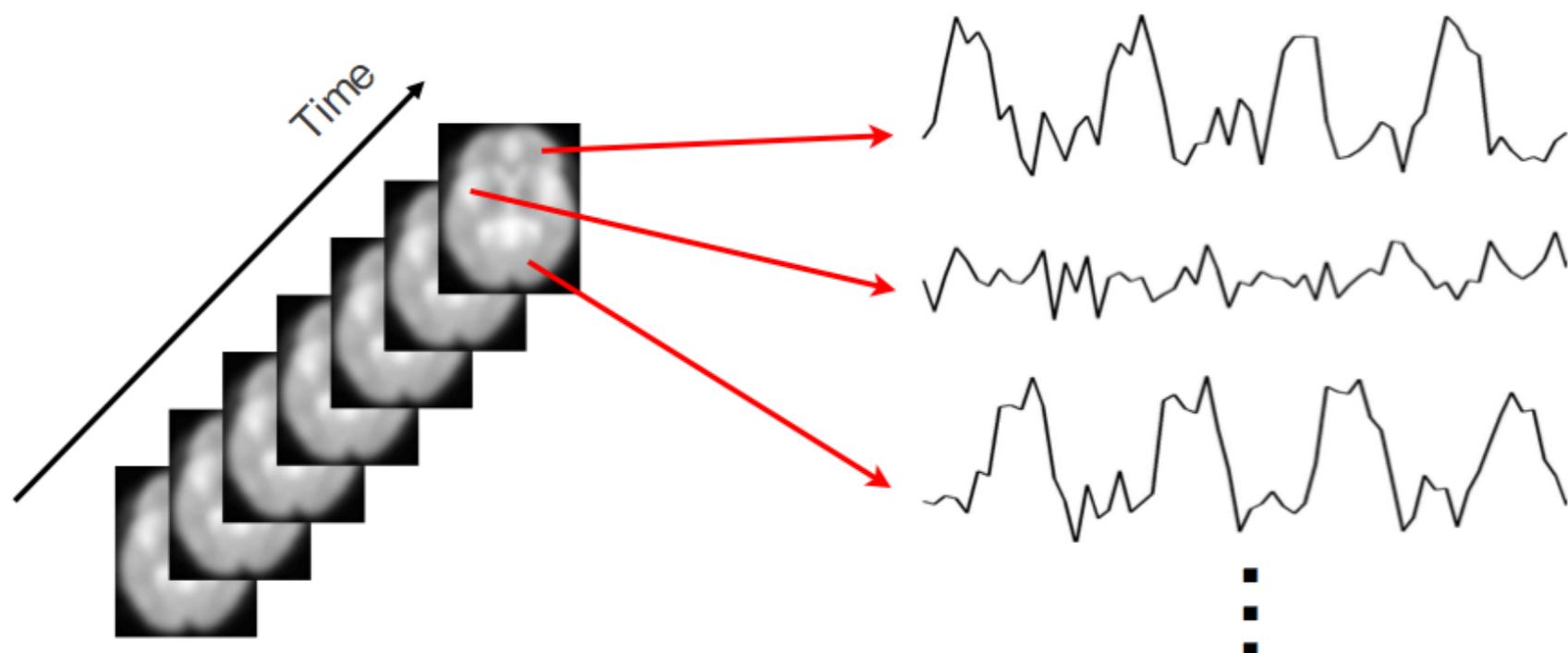
fMRI paradigms

- Task-based fMRI
 - Can we identify which parts of the brain are active (or inactive)?
Not feasible for babies!!
 - When performing different tasks
 - Requires stimuli
- Resting State fMRI
 - What does the brain do when it is 'doing nothing'?
 - No stimulus needed

The fMRI signal.



The fMRI signal.



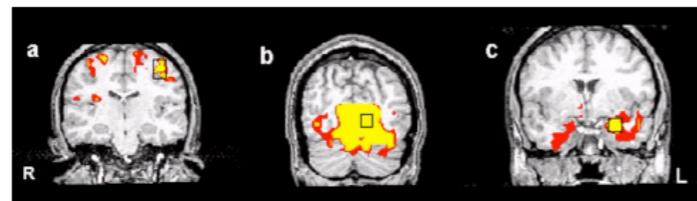
rfMRI analysis

- Original data very high dimensional and noisy
- Makes sense to perform dimensionality reduction as there is clearly structure in the signal
 - ▶ Neighbouring voxels are clustering into regions with coordinated patterns of activity
- Two ways to do this:
 - ▶ Model-free (seed based correlation)
 - ▶ Matrix factorisation e.g. PCA or ICA

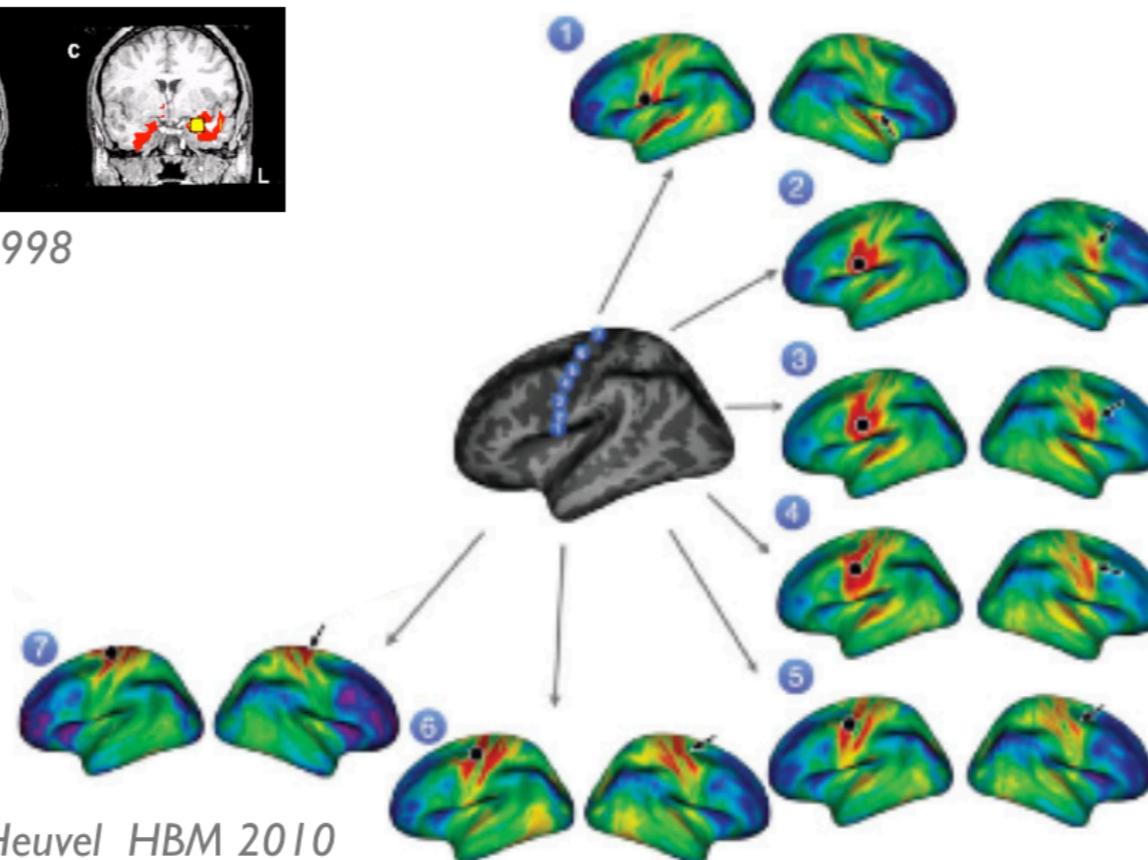
fMRI analysis:

Looking for structure in the data.....

- Different seed locations generate different correlation maps



• Lowe *NeuroImage* 1998



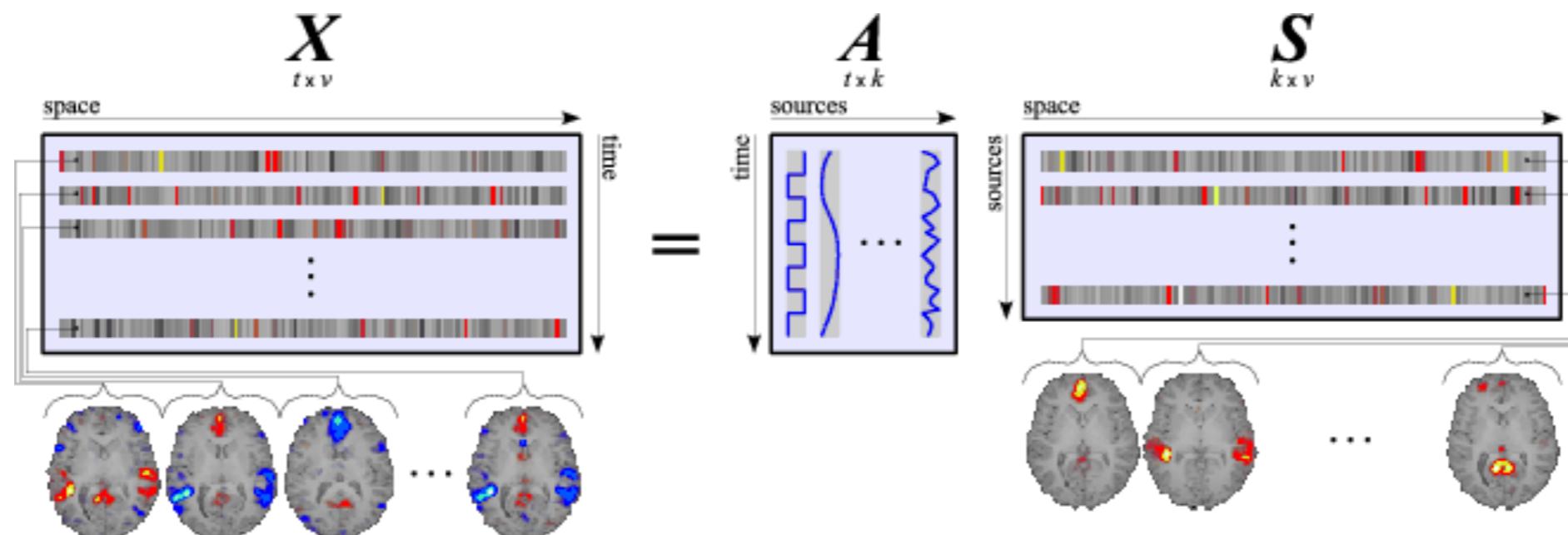
• van den Heuvel *HBM* 2010

Seed-based Correlation analysis

fMRI analysis

ICA of rFMRI

- Decompose data into a set of spatial maps and component time courses



Group ICA

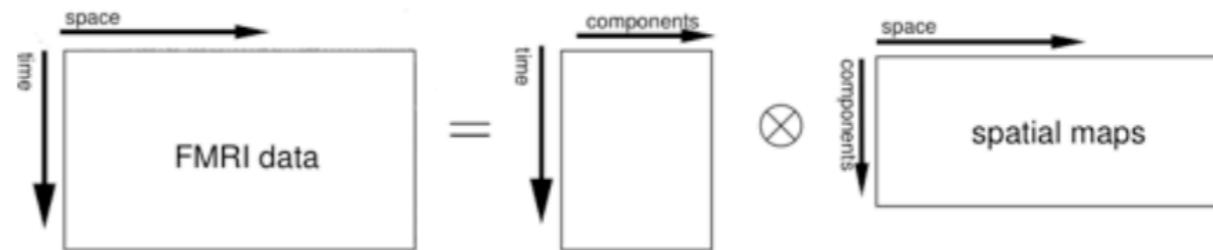
- Boosts signal to noise
- Finds consistent pattern of networks across subjects

Single-Session ICA

each ICA component comprises:



spatial map & timecourse



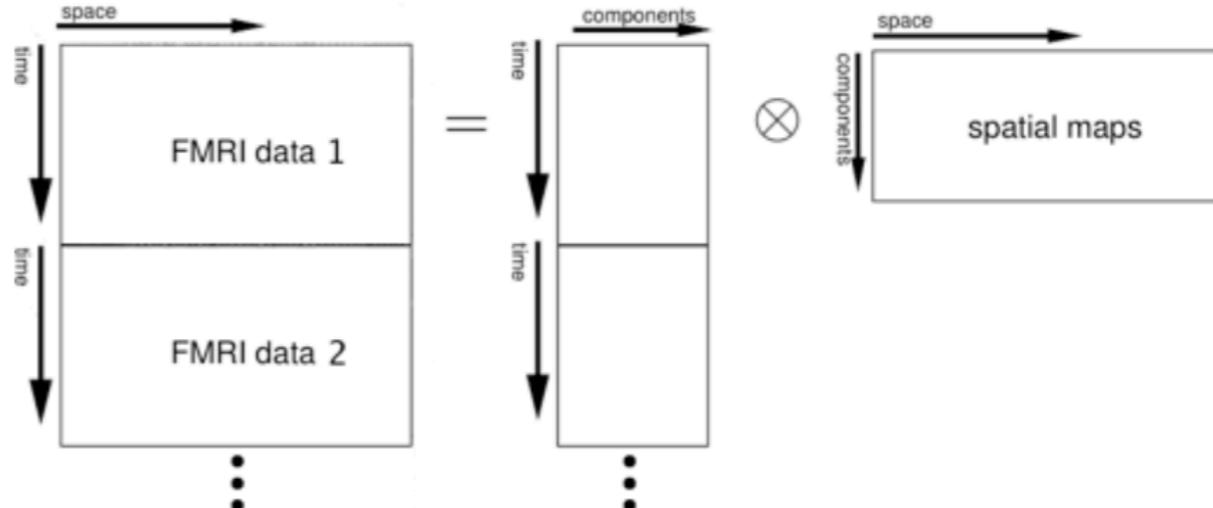
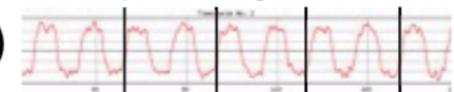
Multi-Session or Multi-Subject ICA: Concatenation approach

each ICA component comprises:



spatial map & timecourse

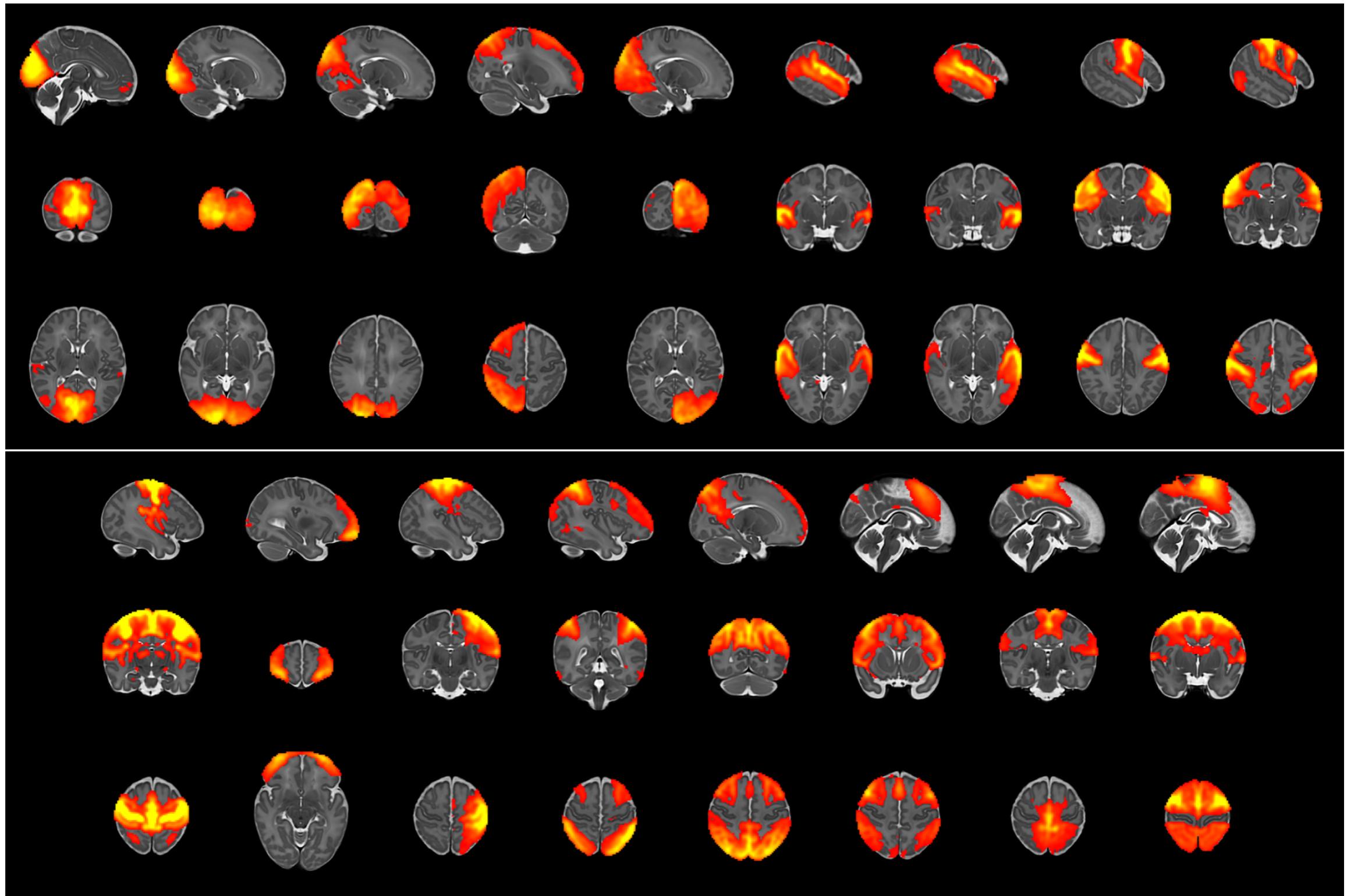
(that can be split up into subject-specific
chunks)



Neonatal fMRI Pipeline

(n=242)

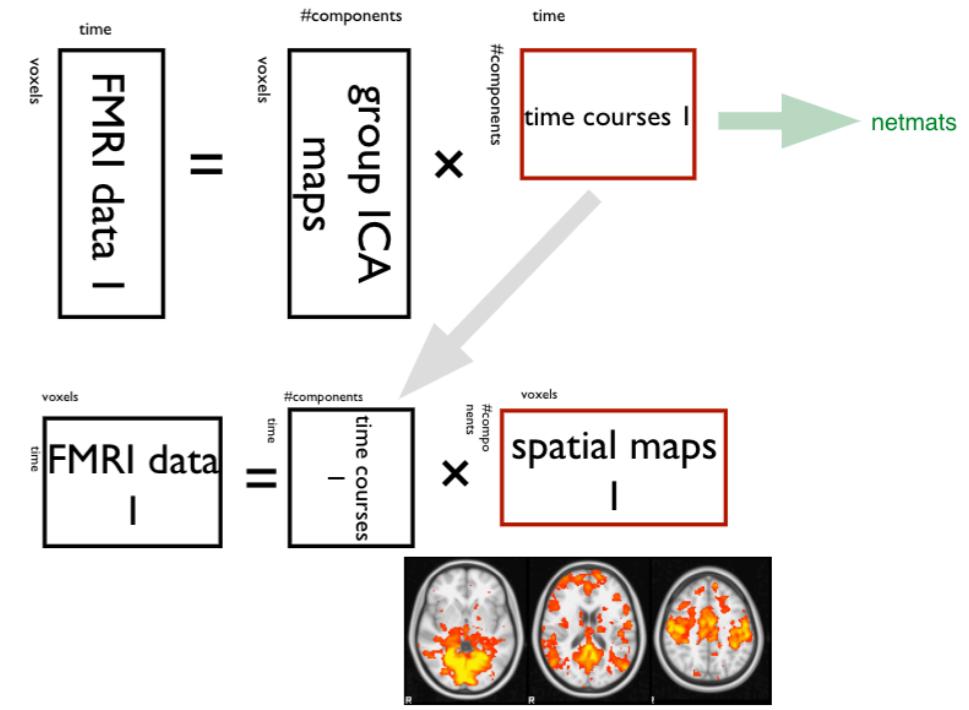
17 Profumo Modes



Dual Regression

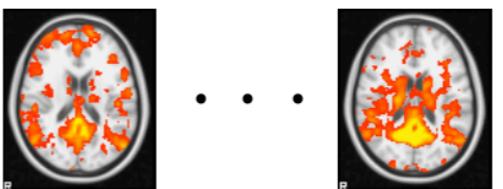
Group-based analysis boosts SNR

- **dr_stage1_subject[#SUB].txt** - the *timeseries* outputs of stage 1 of the dual-regression.

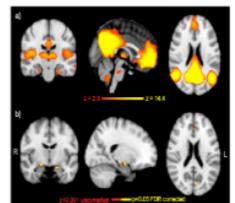


- **dr_stage2_subject[#SUB].nii.gz** - the *spatial maps* outputs of stage 2 of the dual-regression.

- **dr_stage2_ic[#ICA].nii.gz** - the re-organised parameter estimate images



- **dr_stage3_ic[#ICA]_tstat[#CON].nii.gz** - the output from randomise (corrected for mc across voxels but not across #components!!)



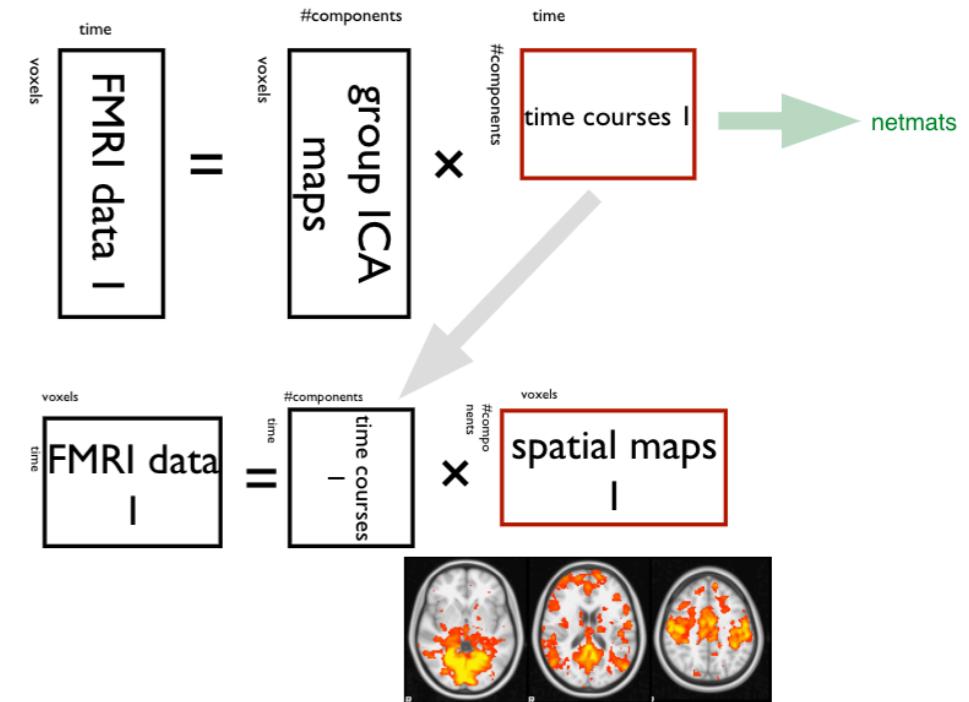
Dual Regression

Group-based analysis boosts SNR

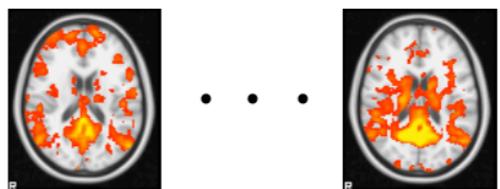
BUT reduces capacity to capture true variance

- **dr_stage1_subject[#SUB].txt** - the *timeseries* outputs of stage 1 of the dual-regression.

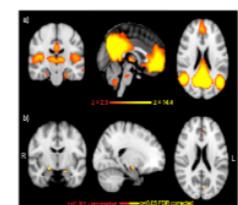
- **dr_stage2_subject[#SUB].nii.gz** - the *spatial maps* outputs of stage 2 of the dual-regression.



- **dr_stage2_ic[#ICA].nii.gz** - the re-organised parameter estimate images



- **dr_stage3_ic[#ICA]_tstat[#CON].nii.gz** - the output from randomise (corrected for mc across voxels but not across #components!!)

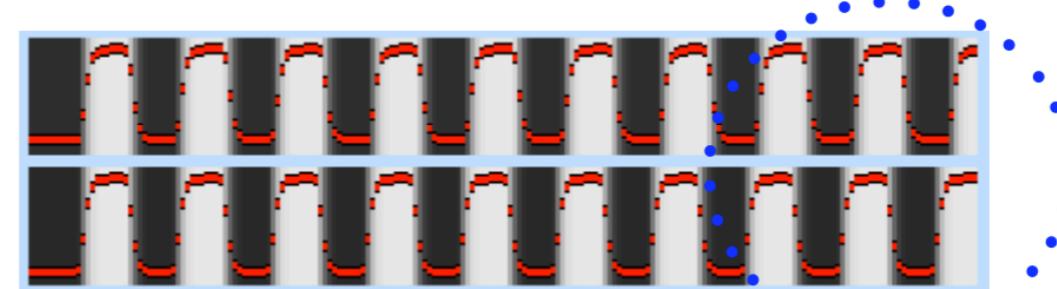
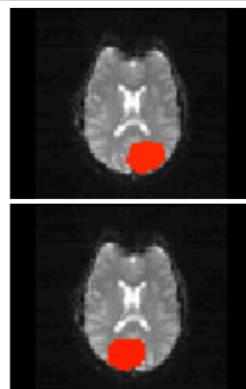




PCA vs. ICA ?

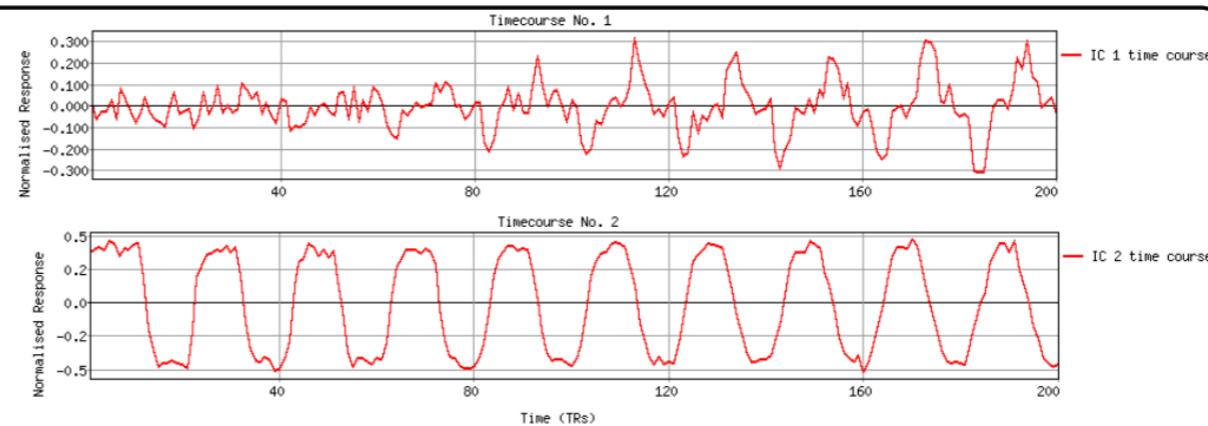
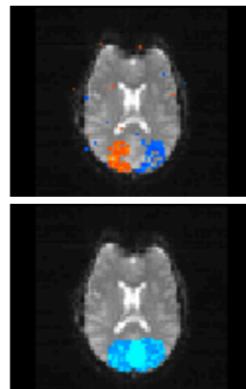
Simulated Data

(2 components, slightly different timecourses)



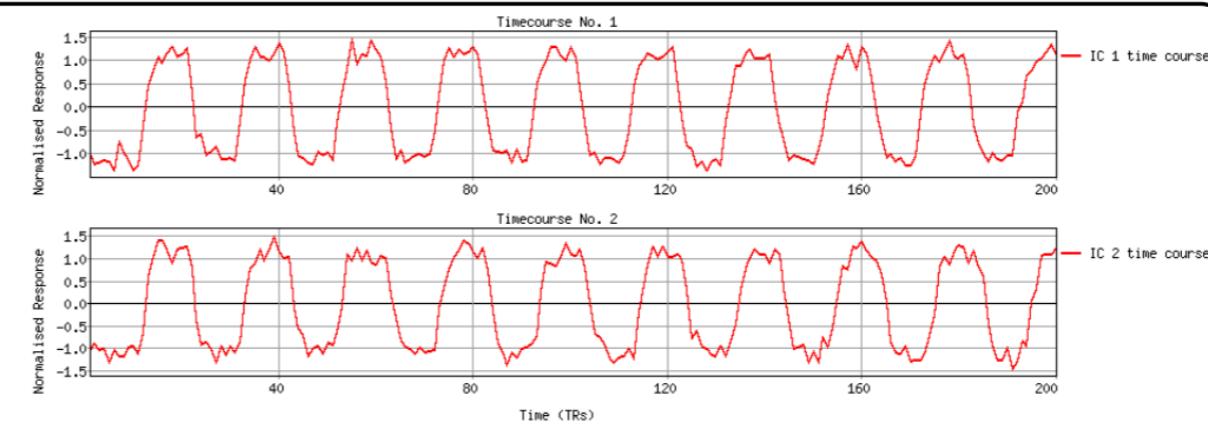
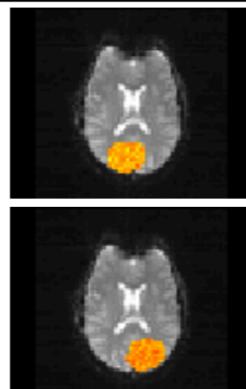
PCA

- Timecourses orthogonal
- Spatial maps and timecourses “wrong”



ICA

- Timecourses non-co-linear
- Spatial maps and timecourses “right”



Relation between the dHCP and HCP

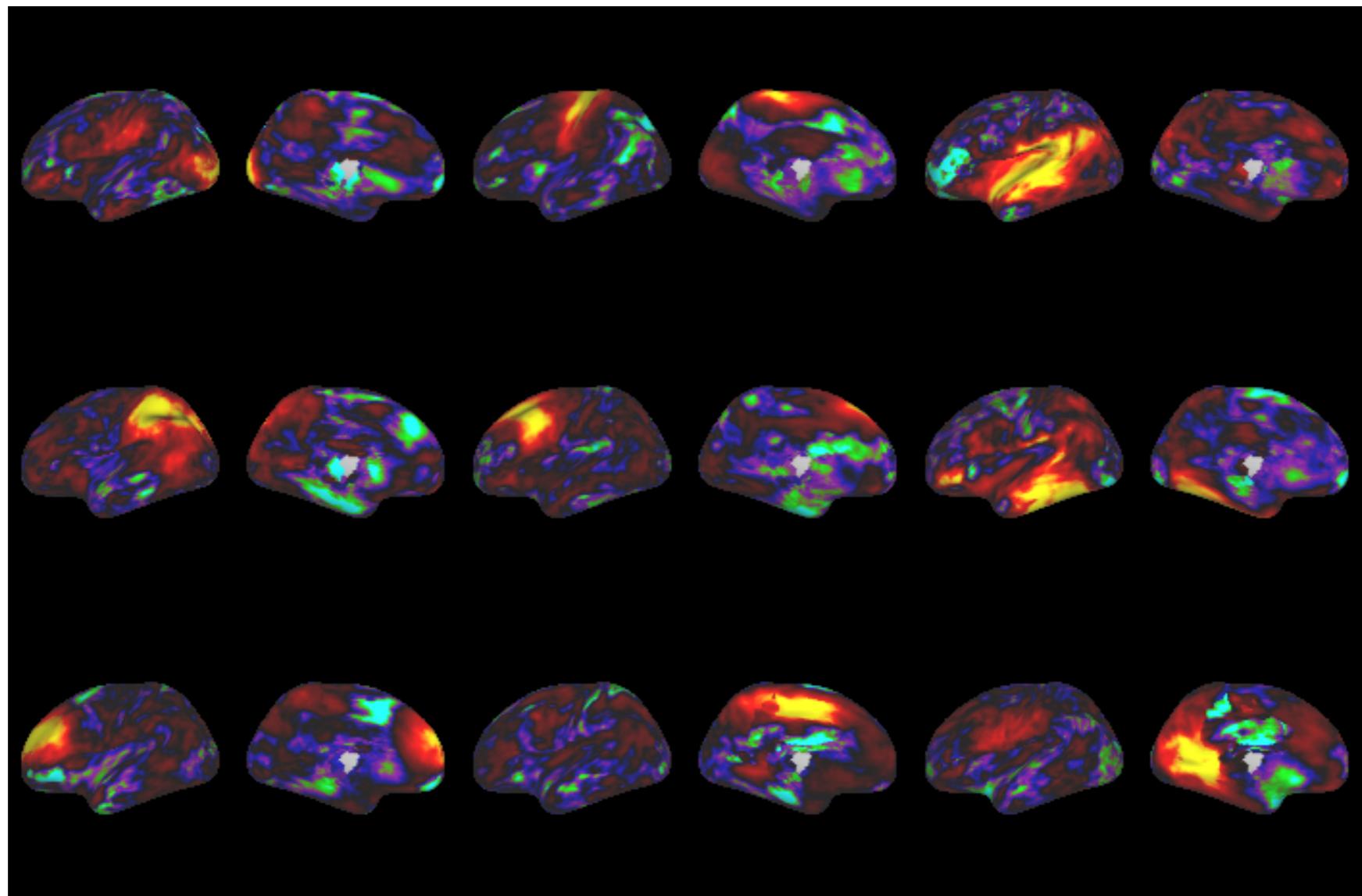
Table 3

Comparison between HCP and dHCP pipelines.sss

	HCP	dHCP
Image Resolution	0.7 mm^3	0.8 mm^3 (0.5 mm^3 after reconstruction)
Total scanning time	4 h	76 min
Preprocessing		
Gradient Distortion Correction	Yes	No
Read-out distortion correction	Yes	No
Brain Extraction	Propagation of atlas mask	BET
T1 - T2 registration	BBR	Rigid Alignment, BBR
Bias Correction	$\sqrt{T1*T2}$	N4
Segmentation/Surface extraction		
Performed on	T1	T2
Tissue Segmentation	FreeSurfer	Draw-EM
White and Pial Surface Extraction	Modified FreeSurfer	Schuh et al. (2017)
Surface Inflation	FreeSurfer	FreeSurfer re-implementation
Spherical Projection	FreeSurfer	spherical MDS
Myelin Mapping	T1/T2	T1/T2

HCP rfMRI is MUCH high spatial and temporal resolution

Examples of neonatal surface-based ICA



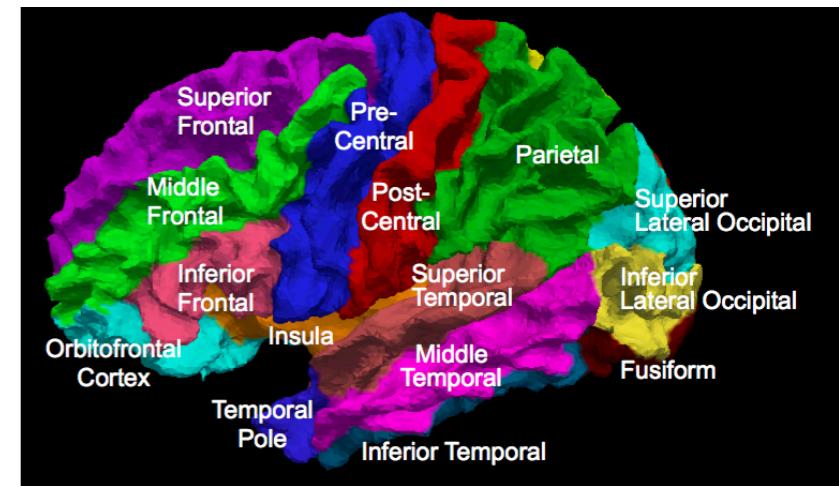
Neonatal RSNs: Developing Human Connectome Project (dHCP)

**Adult HCP data can resolve 200 or more clean RSNs (see
`wb_view`)**

Building connectivity networks: nodes

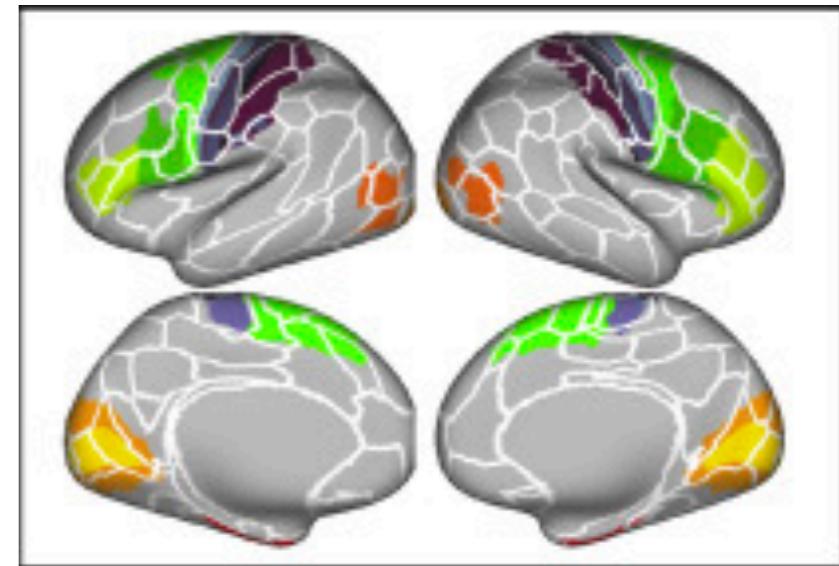
1. Anatomical ROIs (cortical folding patterns)

- ▶ Known not to correlate with patterns of functional organisation across much of the brain



2. Data-driven:

- ▶ Clustering of rfMRI/dMRI signals
- ▶ Signals are noisy, model underlying neuronal connections in a simplified and indirect way



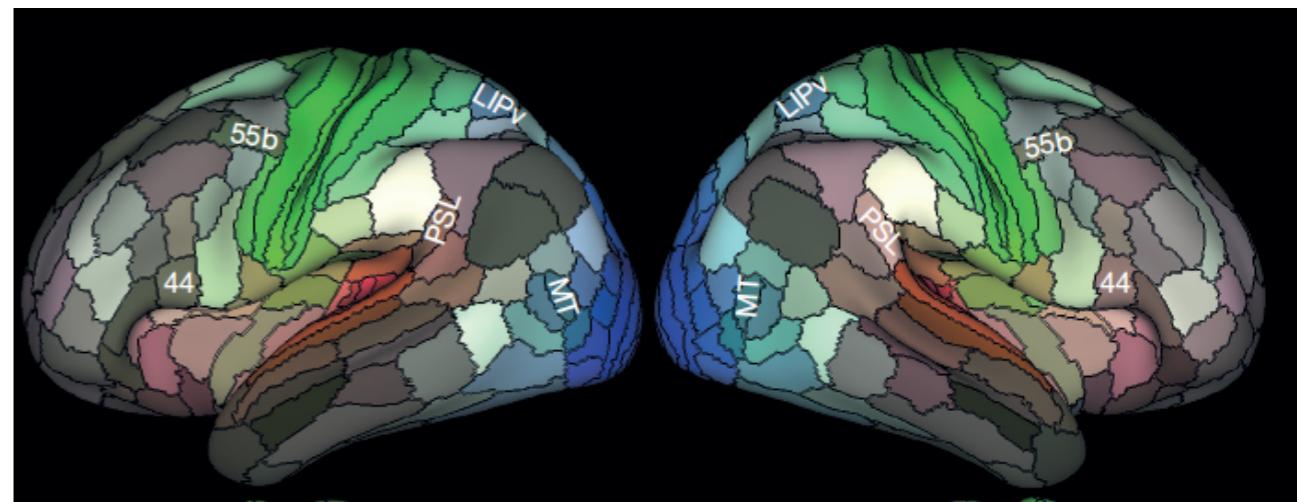
Parisot et al. 2017

Building connectivity networks: nodes

3. Hand annotated:

- Limited ground truth understanding of how the brain is organised
- Assumes expert knowledge of neuroanatomy
- Highly time consuming

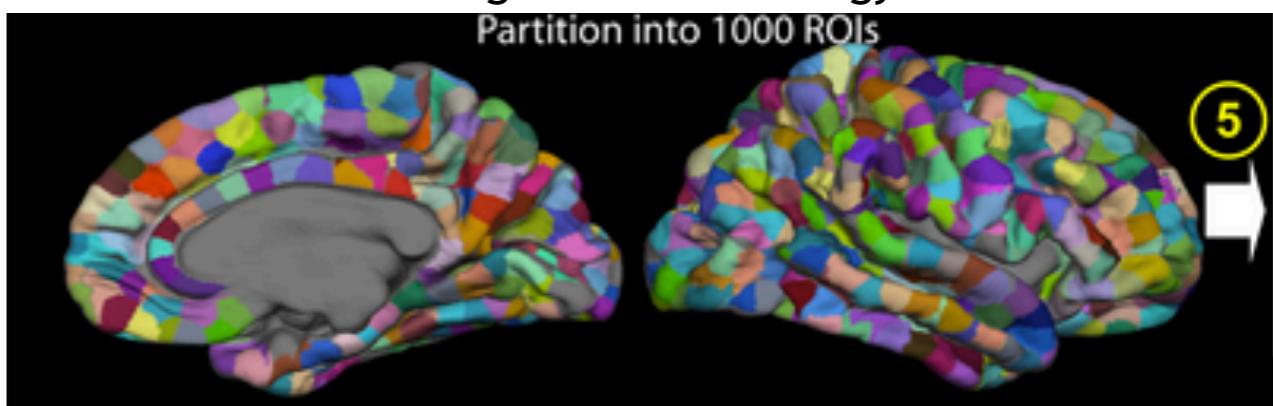
Glasser et al. Nature 2016



4. Random

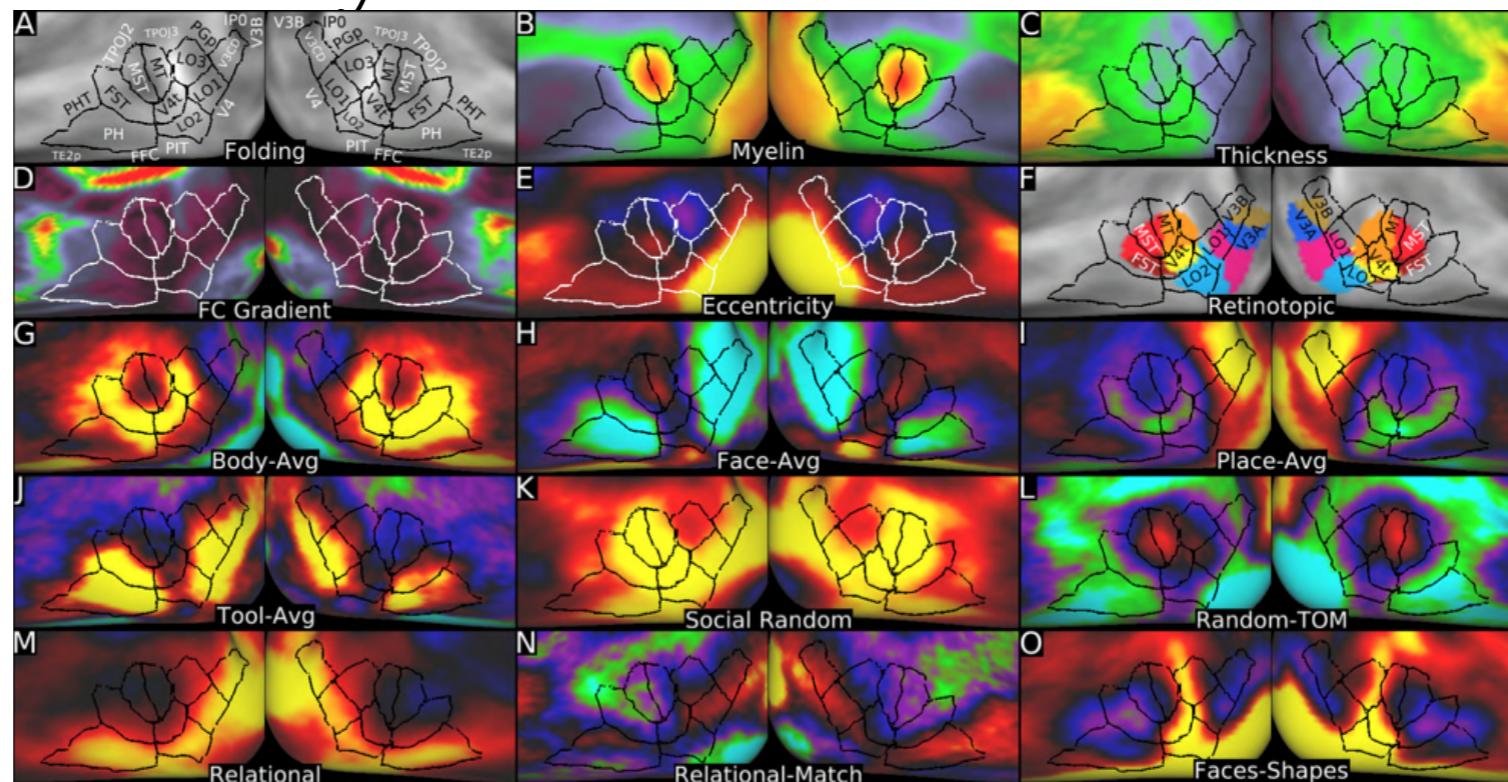
- Heavily reliant on accurate surface registration

Hagmann Plos Biology 2008



Building connectivity networks: nodes

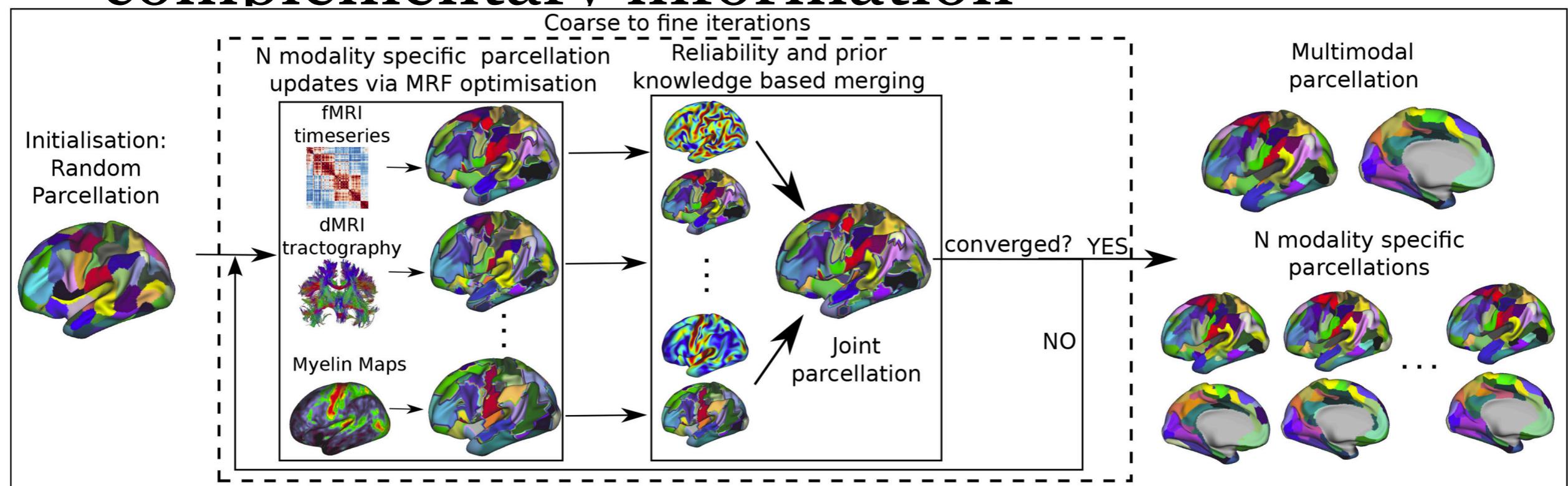
- Multi-modality information provides complementary information



Glasser et al. Nature 2016

Building connectivity networks: nodes

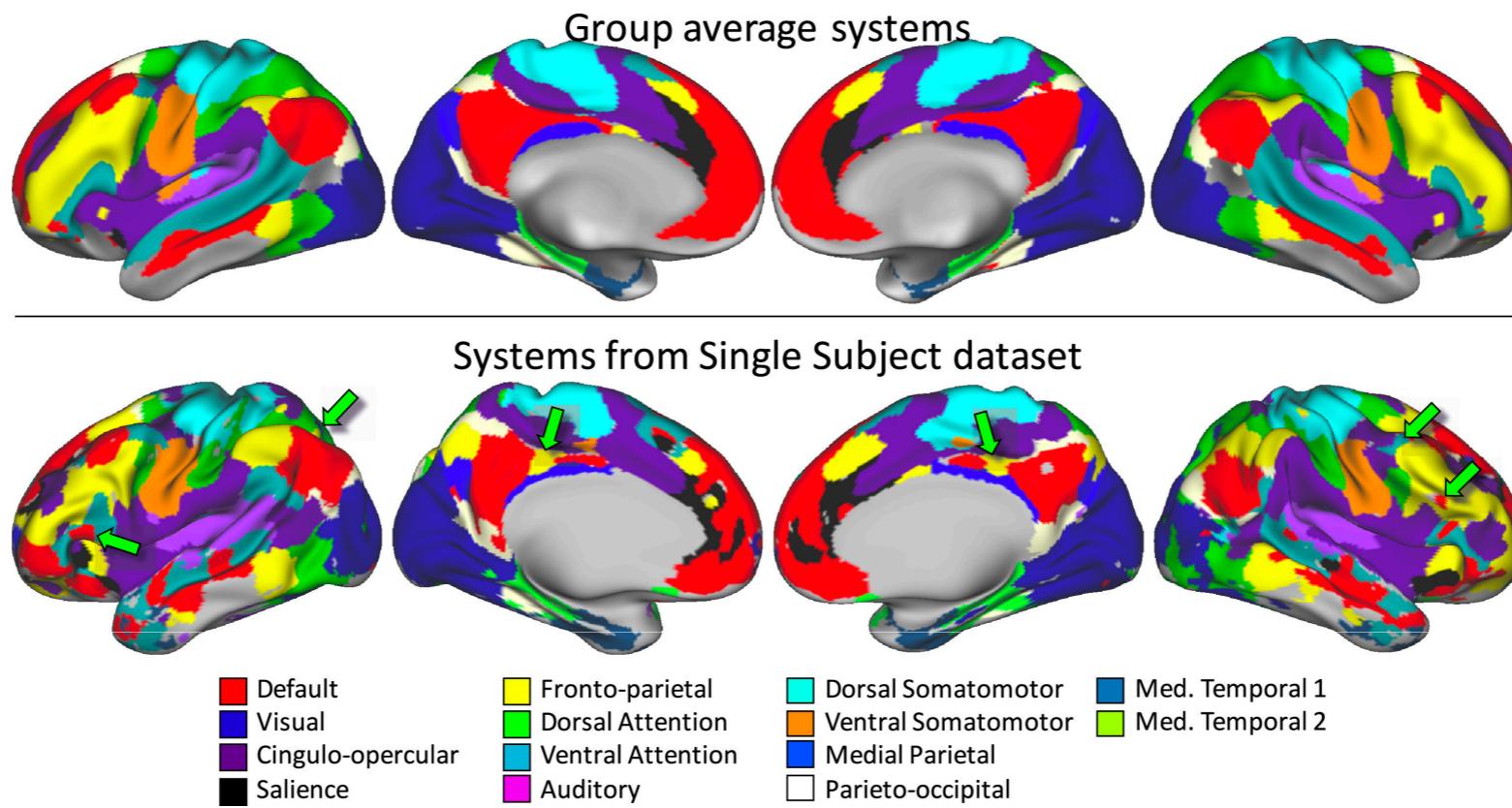
- Multi-modality information provides complementary information



Parisot et al. 2017

Building connectivity networks: Capturing inter-subject variability

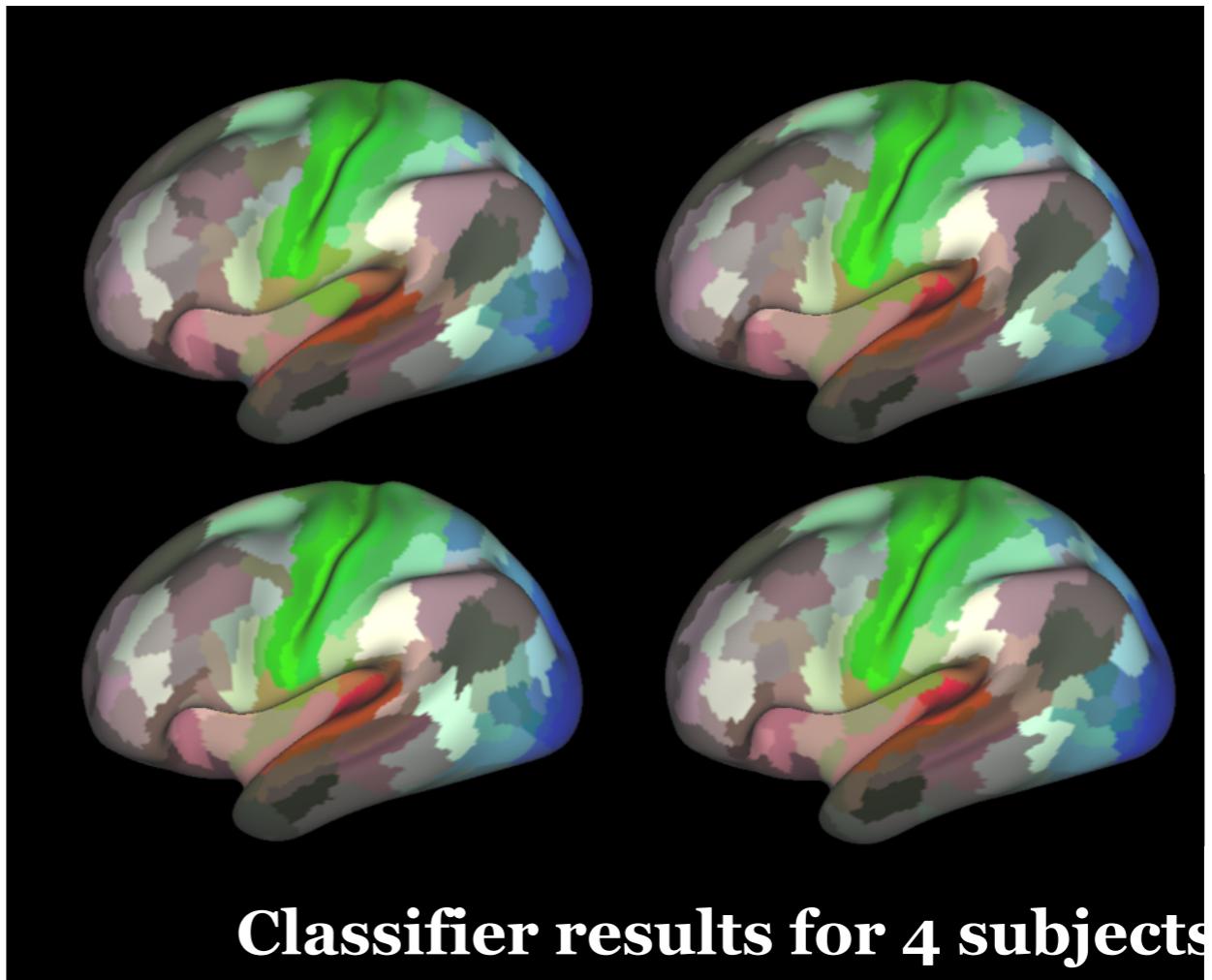
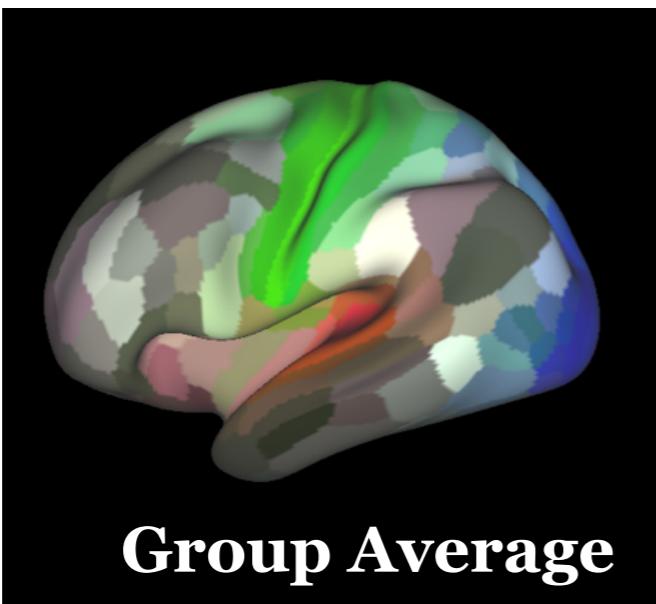
- Functional organisation varies topologically



Gordon, Evan M., et al. "Individual-specific features of brain systems identified with resting state functional correlations." *NeuroImage* 146 (2017): 918-939.

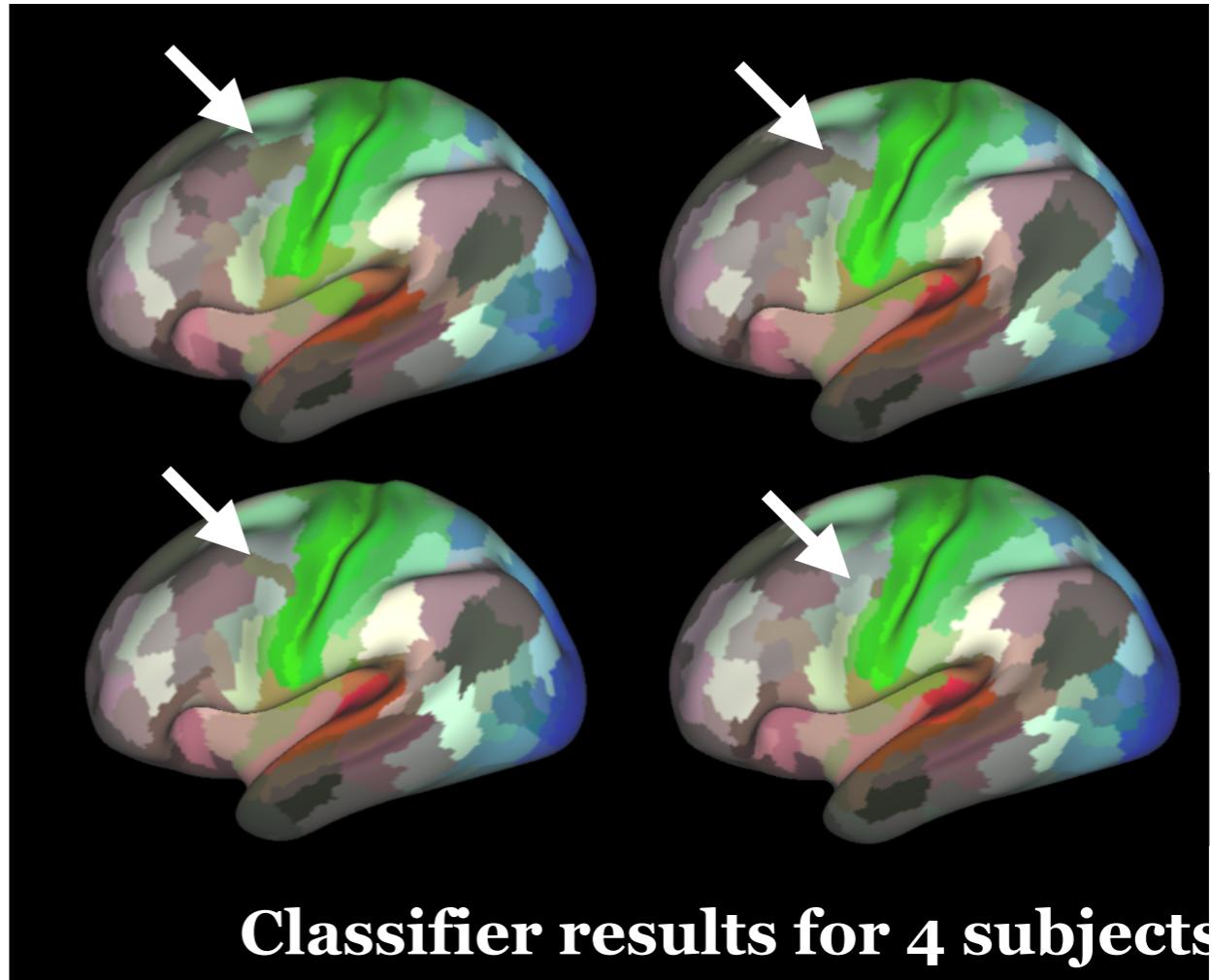
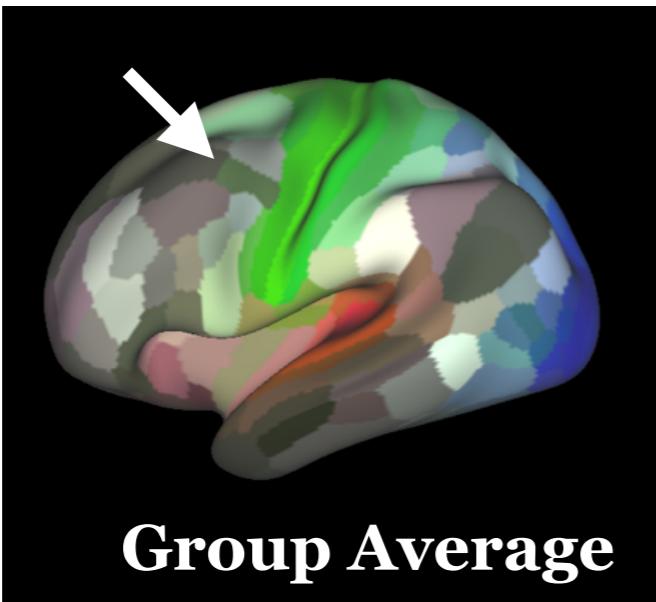
Building connectivity networks: Capturing inter-subject variability

- Without enforcing global consistency how do we compare?



Building connectivity networks: Capturing inter-subject variability

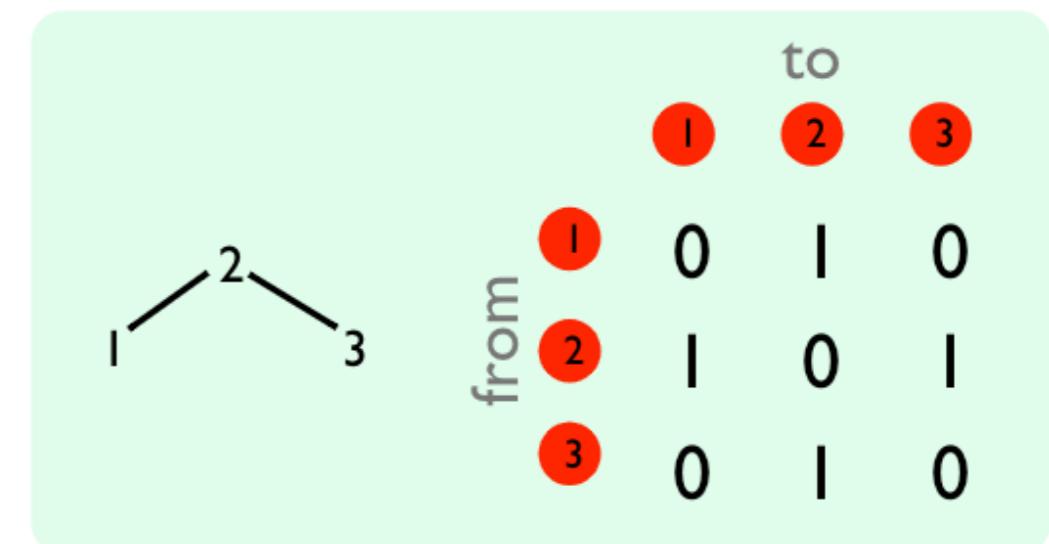
- Without enforcing global consistency how do we compare?



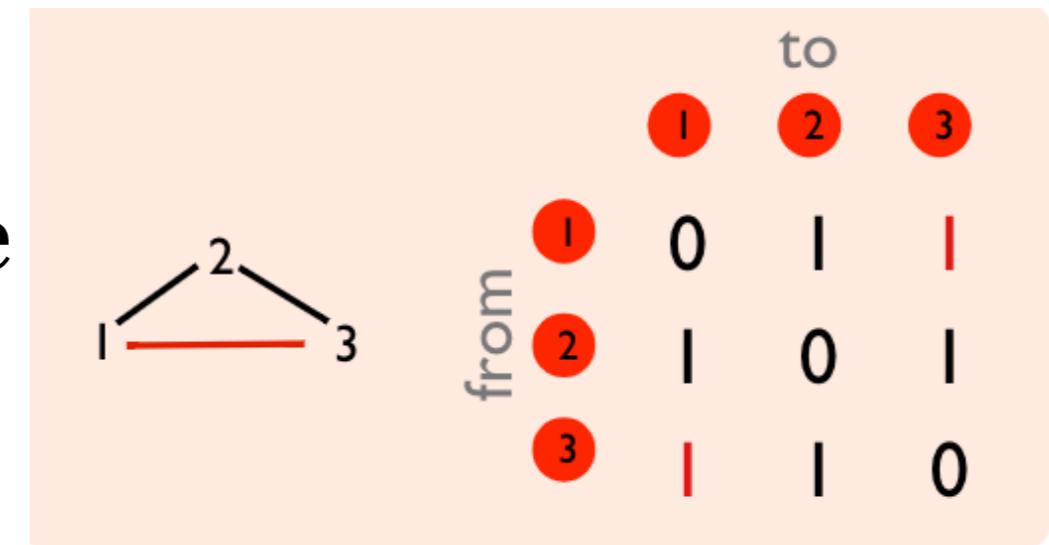
Building connectivity networks: Edge weights

- Full or Partial Correlation?

Ground truth →



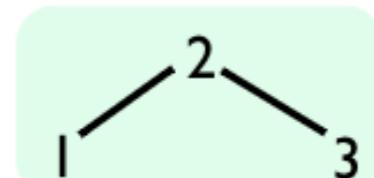
Full correlation will approximate →



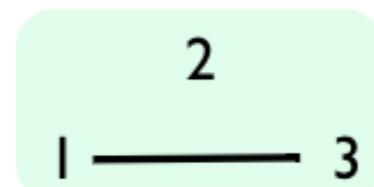
Building connectivity networks: Edge weights

- Partial Correlation (Inverse covariance)

► Closer to direct connectivity?



vs.



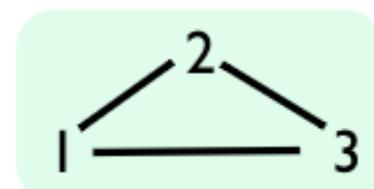
- Methods:

► Before correlating 1 and 3, first regress 2 out of both (“orthogonalise wrt 2”)

► Estimate sparse-penalised inverse covariance matrix

► Graph Lasso (L1 penalty)

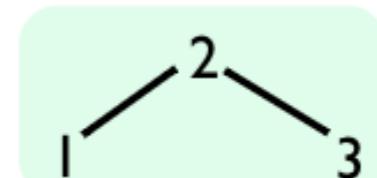
vs.



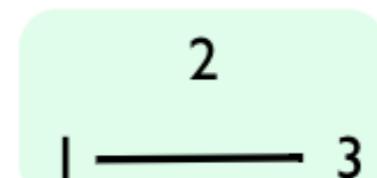
Building connectivity networks: Edge weights

- Partial Correlation (Inverse covariance)

► Closer to direct connectivity?



vs.



- Methods:

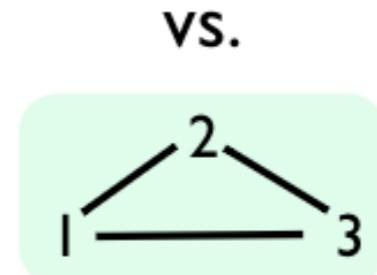
► Before correlating 1 and 3, first regress 2 out of both (“orthogonalise wrt 2”)

► Estimate sparse-penalised inverse covariance matrix

► Graph Lasso (L1 penalty)

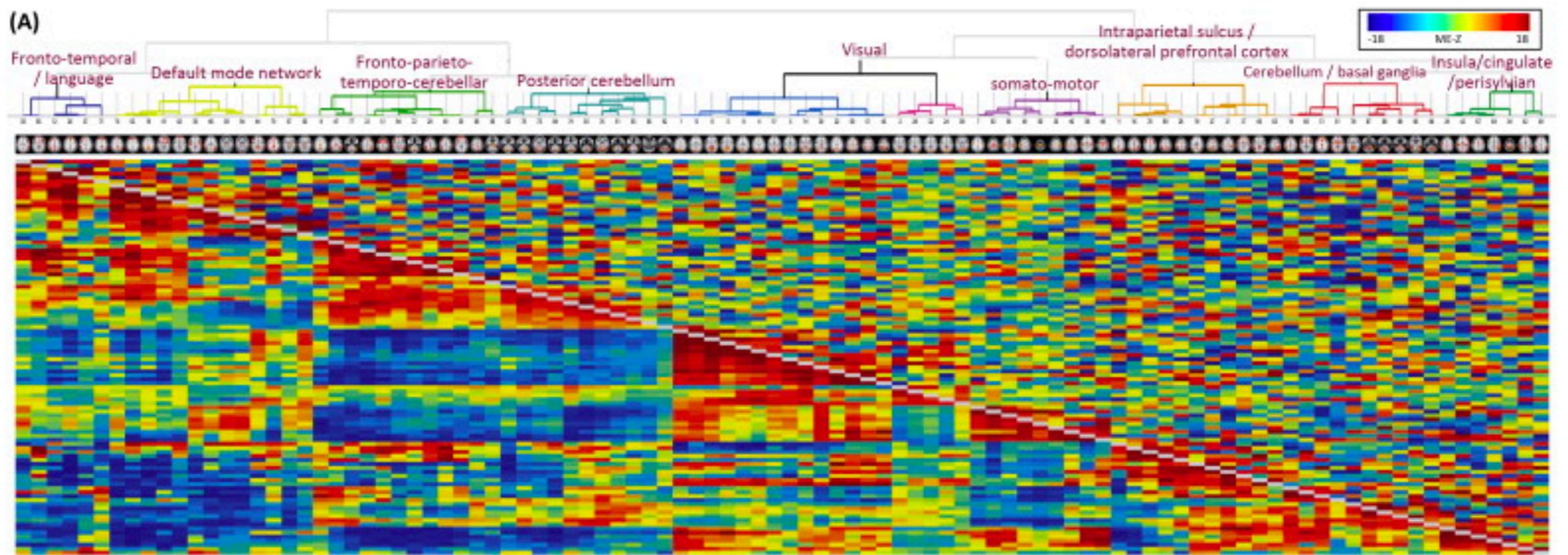


Very costly to calculate



Building connectivity networks: Edge weights

- Full or Partial Correlation?



Smith et al. Trends in Cognitive Science, 2013

Predicting behavioural and cognitive traits from brain function

- Functional connectivity is clearly predictive of brain function
- But we don't know why
 - Is it changes to coupling strength of signals?
 - Or is it variations in brain functional organisation and topological structure?
 - Does it make sense to do DL with rfMRI (connectivity)?

Examples

Comparing Connectivity: Unsupervised Learning

Canonical Correlation:

- Explores relationship between two multivariate sets of variables
- For two matrices \mathbf{X} and \mathbf{Y} , where columns \mathbf{X}_i and \mathbf{Y}_i represent different variable sets for some example i (imaging data/demographic variables)
- Wish to find 2 new sets of basis vectors \mathbf{A} and \mathbf{B} (one for \mathbf{X} , one for \mathbf{Y}) that will rotate data into new basis that maximises correlations:
 - $\mathbf{A}'\mathbf{X}$ and $\mathbf{B}'\mathbf{Y}$ maximise $\rho = \text{corr}(\mathbf{A}'\mathbf{X}, \mathbf{B}'\mathbf{Y})$

Examples

Comparing Connectivity: Unsupervised Learning

Canonical Correlation:

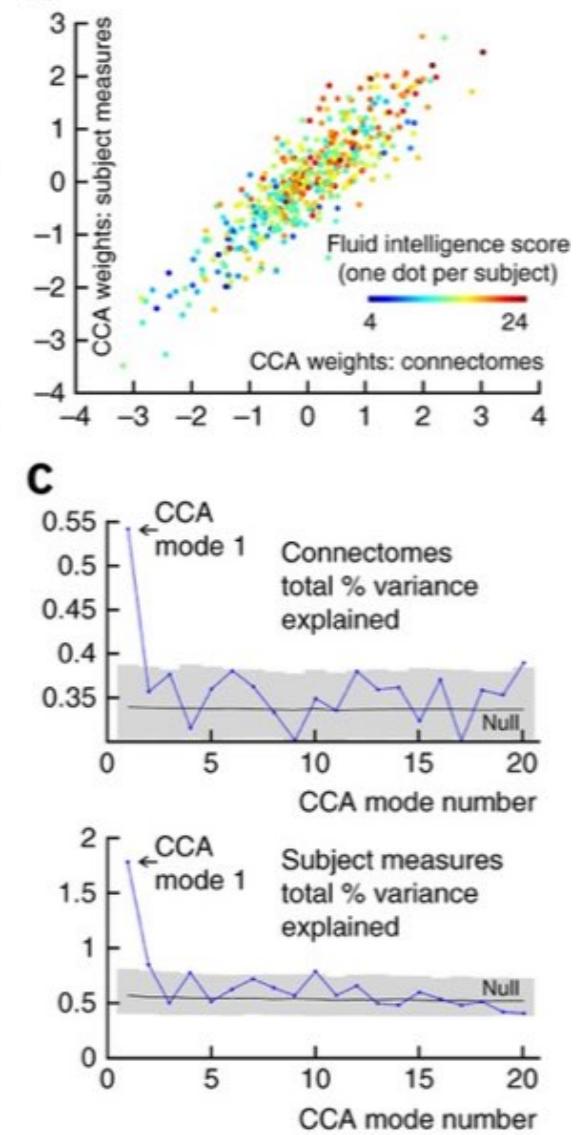
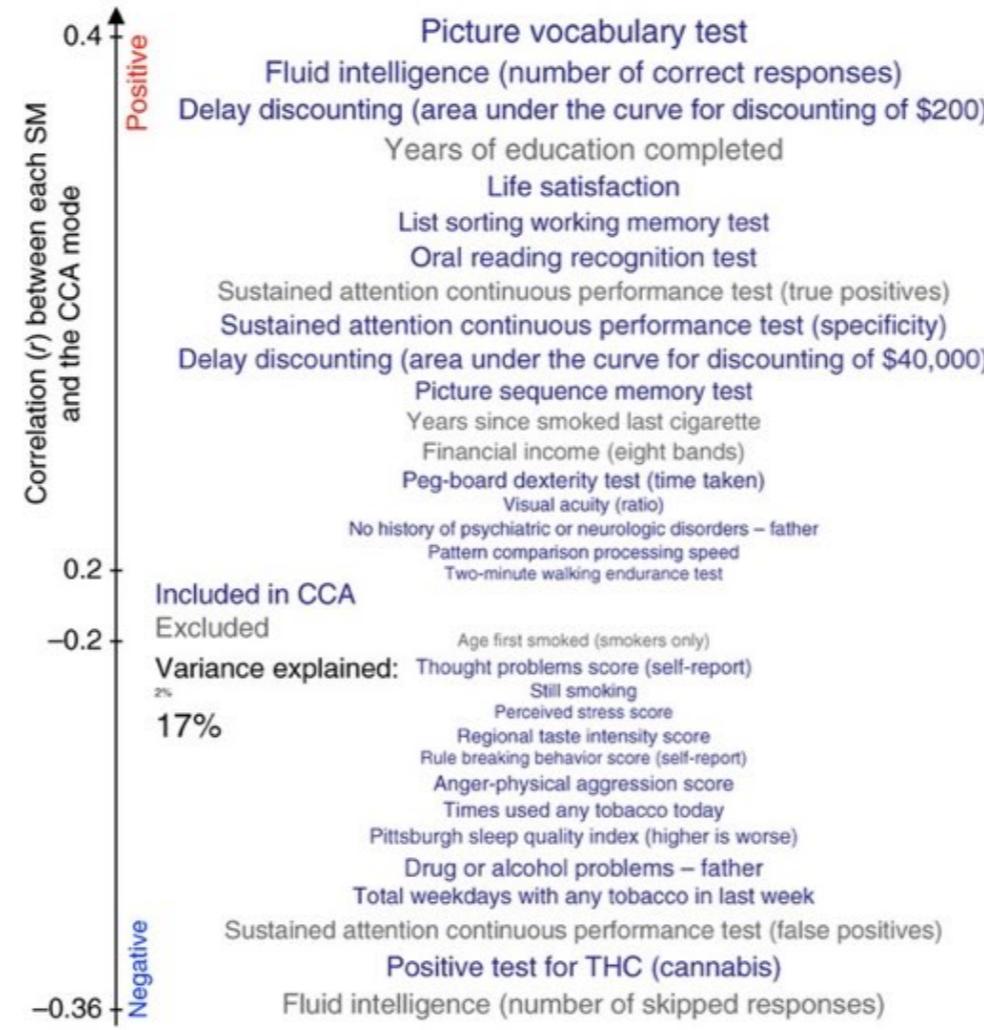
- Explores relationship between two multivariate sets of variables
- For two matrices \mathbf{X} and \mathbf{Y} , where columns \mathbf{X}_i and \mathbf{Y}_i represent different variable sets for some example i (imaging data/demographic variables)
- Wish to find 2 new sets of basis vectors \mathbf{A} and \mathbf{B} (one for \mathbf{X} , one for \mathbf{Y}) that will rotate data into new basis that maximises correlations:

- $\mathbf{A}'\mathbf{X}$ and $\mathbf{B}'\mathbf{Y}$ maximise $\rho = \text{corr}(\mathbf{A}'\mathbf{X}, \mathbf{B}'\mathbf{Y})$

Latent modes of variation

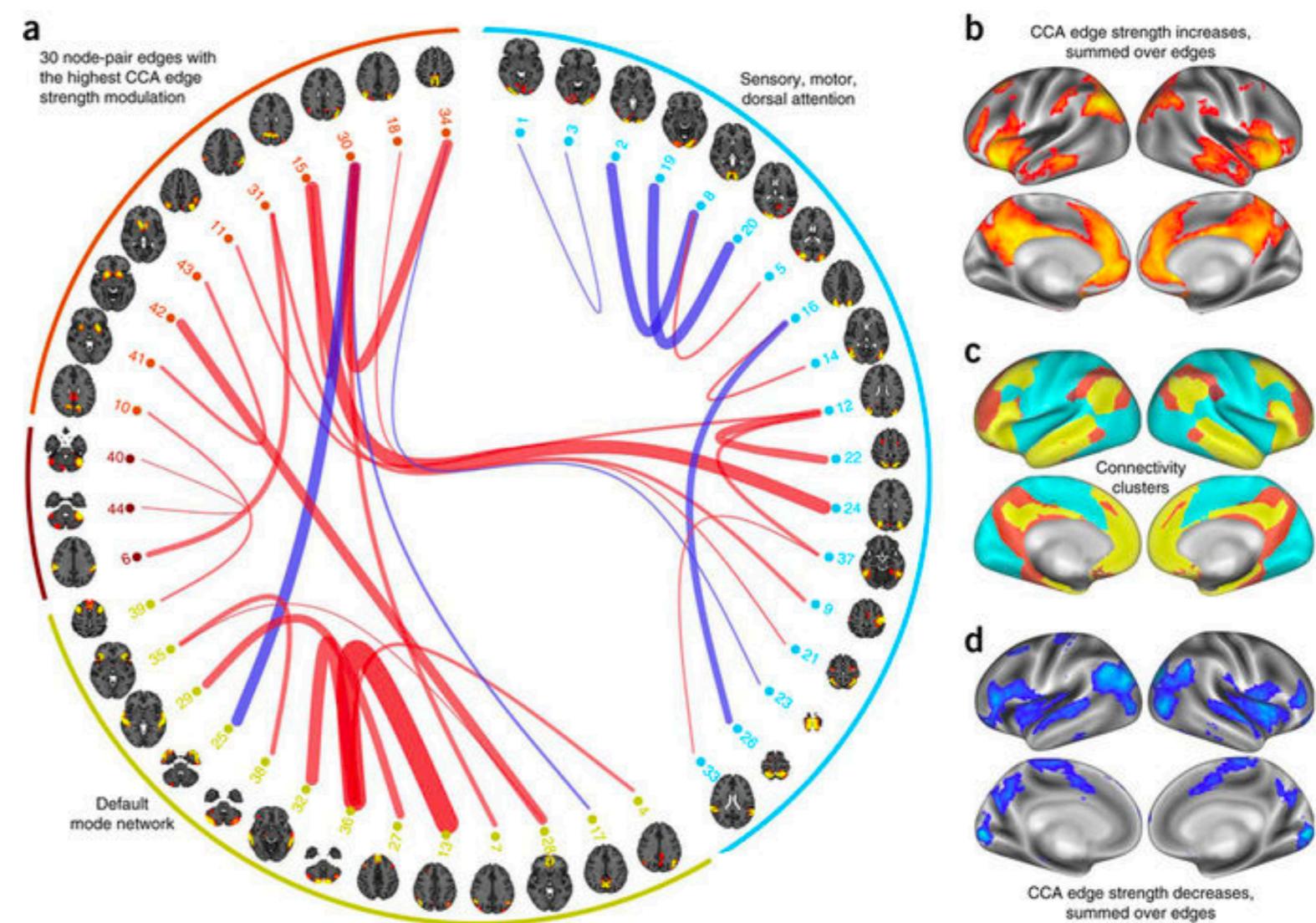
Comparing Connectivity: Unsupervised Learning

- Smith et al. Nature NeuroScience 2015
- Canonical correlation of functional netmats vs HCP demographics



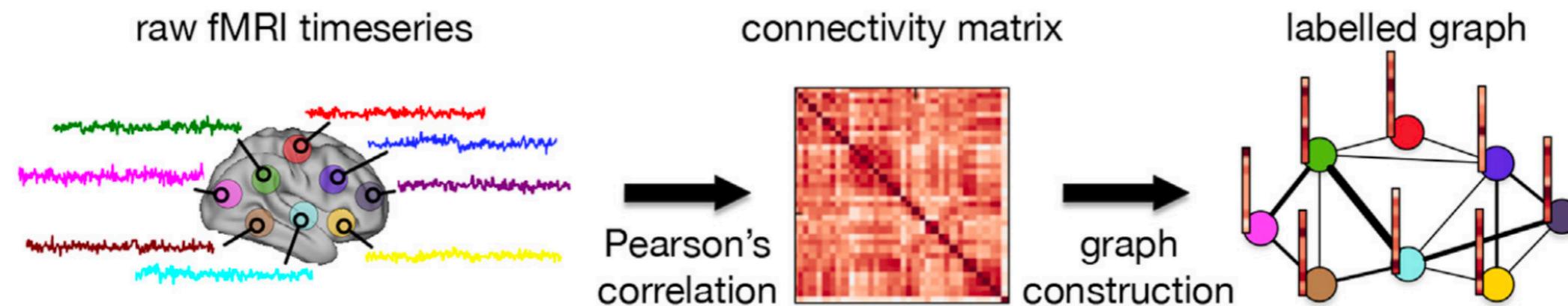
Comparing Connectivity: Unsupervised Learning

- Smith et al. Nature NeuroScience 2015
- Canonical correlation of functional netmats vs HCP demographics



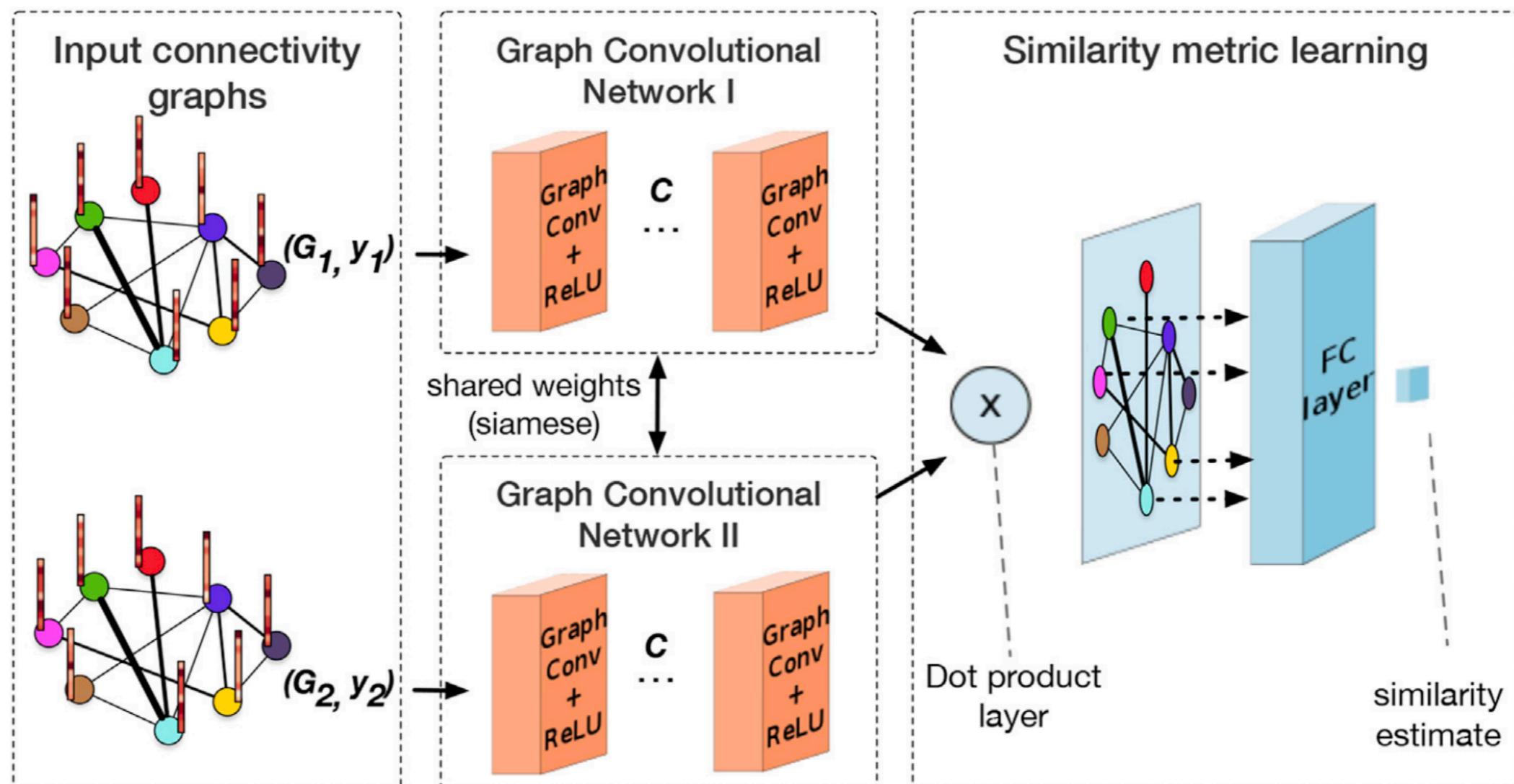
Deep Learning predictions:

Metric learning with spectral graph convolutions on brain connectivity networks, Ktena et al



Deep Learning predictions:

Metric learning with spectral graph convolutions on brain connectivity networks, Ktena et al



(b) Siamese graph convolutional neural network for metric learning. A pair of graphs with the same structure but different signals is fed to this network, which outputs a similarity estimate between the two graphs. A same class (matching) / different class (non-matching) binary label is used for each pair during training.

Deep Learning predictions:

Predicting cognitive scores from resting fMRI data and geometric features of the brain, AA Joshi et al

- fMRI (surface and volume), curvature, sulcal depth and thickness
- Surface data projected to 2D plane
- Use to predict cognitive scores to predict ADHD

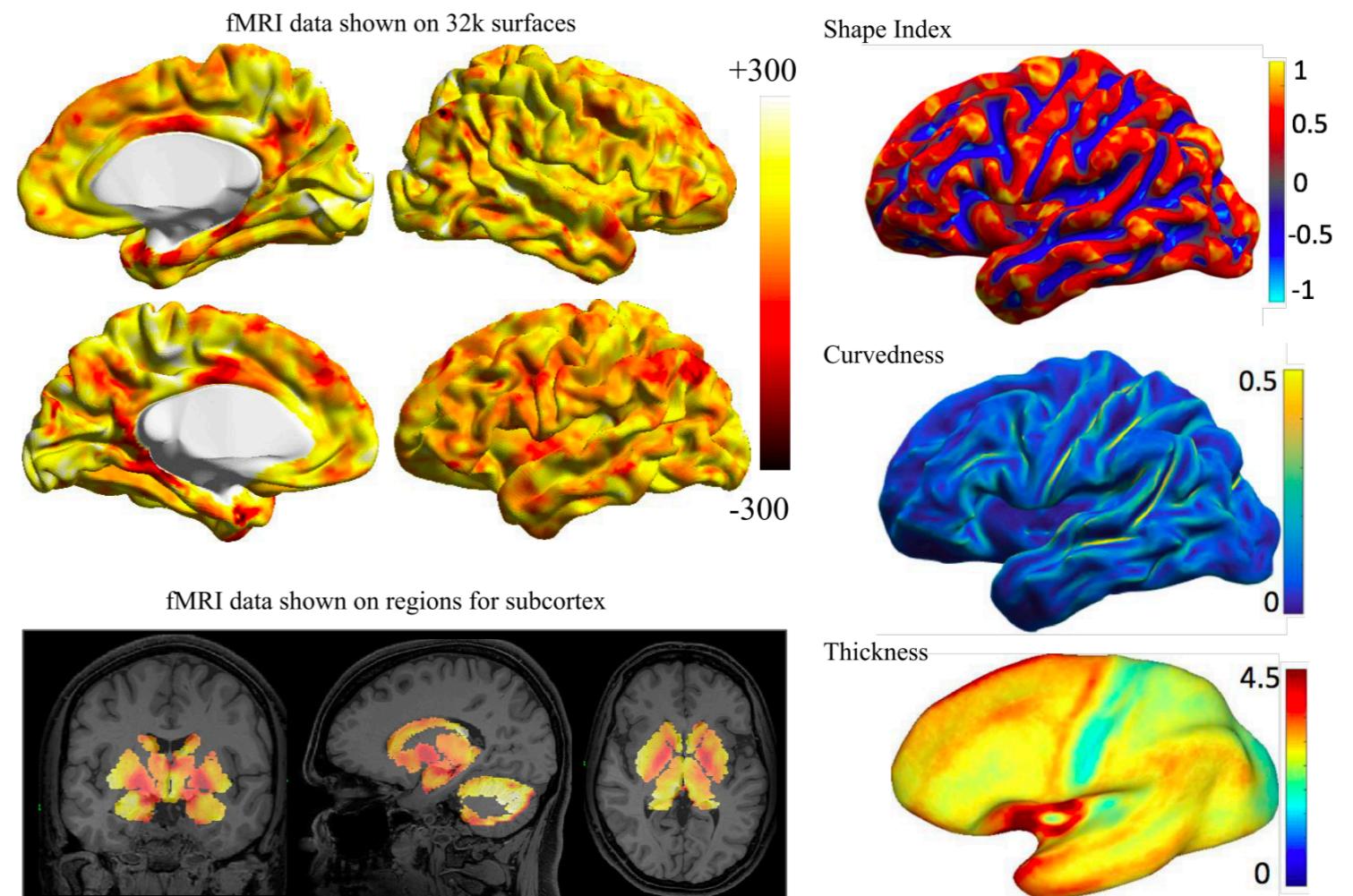


Figure 1. (Left) fMRI data mapped to cortex (upper) and subcortical regions (lower) for grayordinates. (Right) Shape index (S), curvedness (C), and thickness (T).

Deep Learning predictions:

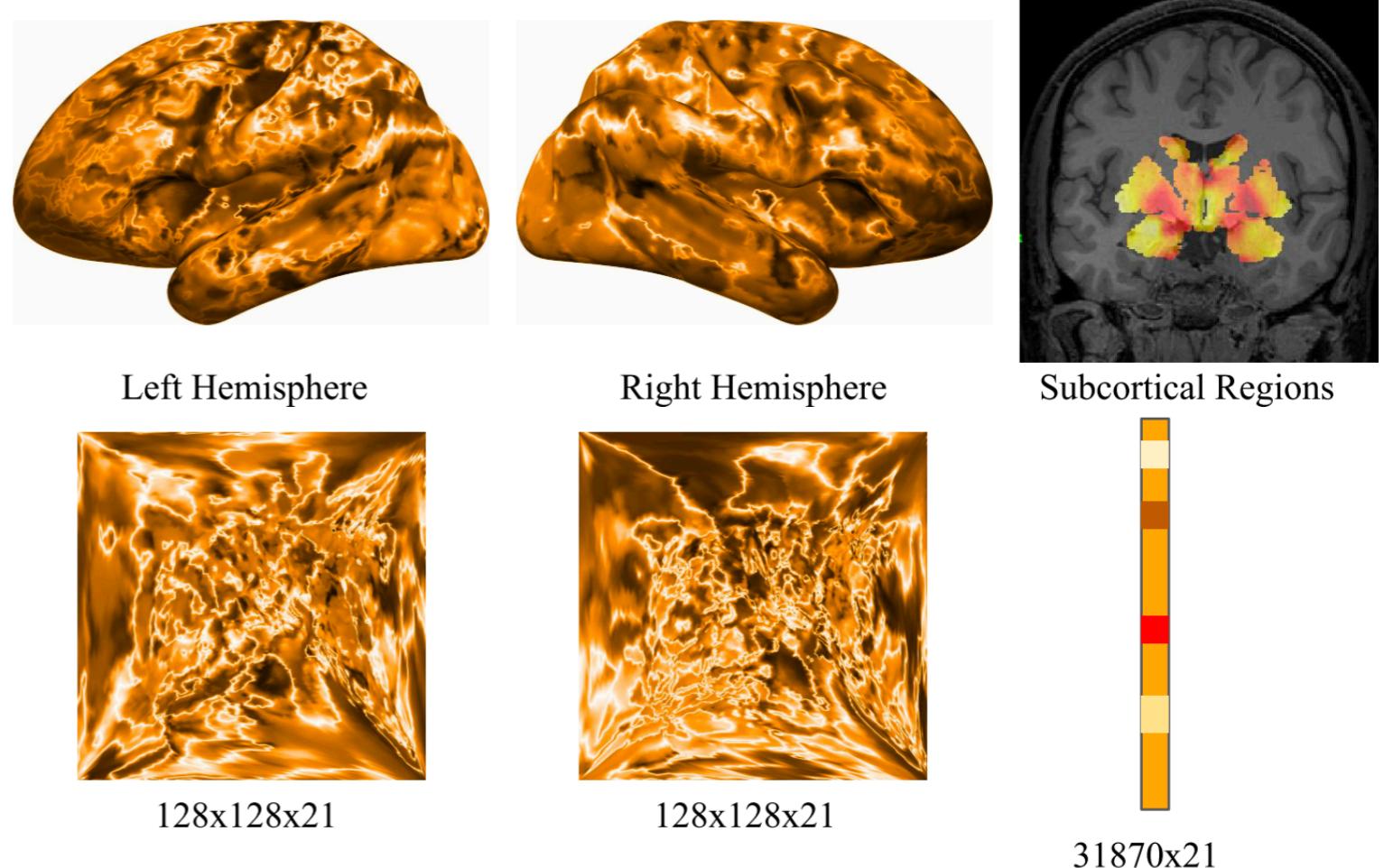
Predicting cognitive scores from resting fMRI data and geometric features of the brain, AA Joshi et al

- fMRI (surface and volume), curvature, sulcal depth and thickness
- Surface data projected to 2D plane
- Use to predict cognitive scores to predict ADHD

Deep Learning predictions:

Predicting cognitive scores from resting fMRI data and geometric features of the brain, AA Joshi et al

- fMRI (surface and volume), curvature, sulcal depth and thickness
- Surface data projected to 2D plane
- Use to predict cognitive scores to predict ADHD



Deep Learning predictions:

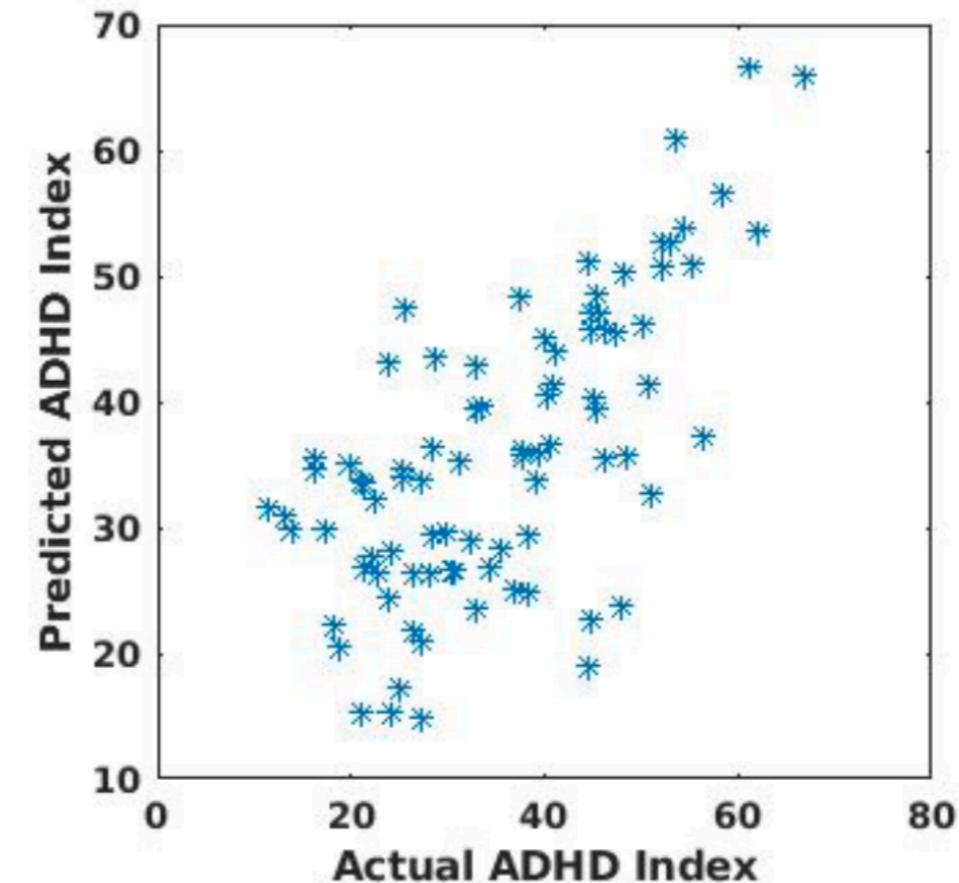
Predicting cognitive scores from resting fMRI data and geometric features of the brain, AA Joshi et al

- fMRI (surface and volume), curvature, sulcal depth and thickness
- Surface data projected to 2D plane
- Use to predict cognitive scores to predict ADHD

Deep Learning predictions:

Predicting cognitive scores from resting fMRI data and geometric features of the brain, AA Joshi et al

- fMRI (surface and volume), curvature, sulcal depth and thickness
- Surface data projected to 2D plane
- Use to predict cognitive scores to predict ADHD



Deep Learning predictions:

Metric learning with spectral graph convolutions on brain connectivity networks, Ktena et al

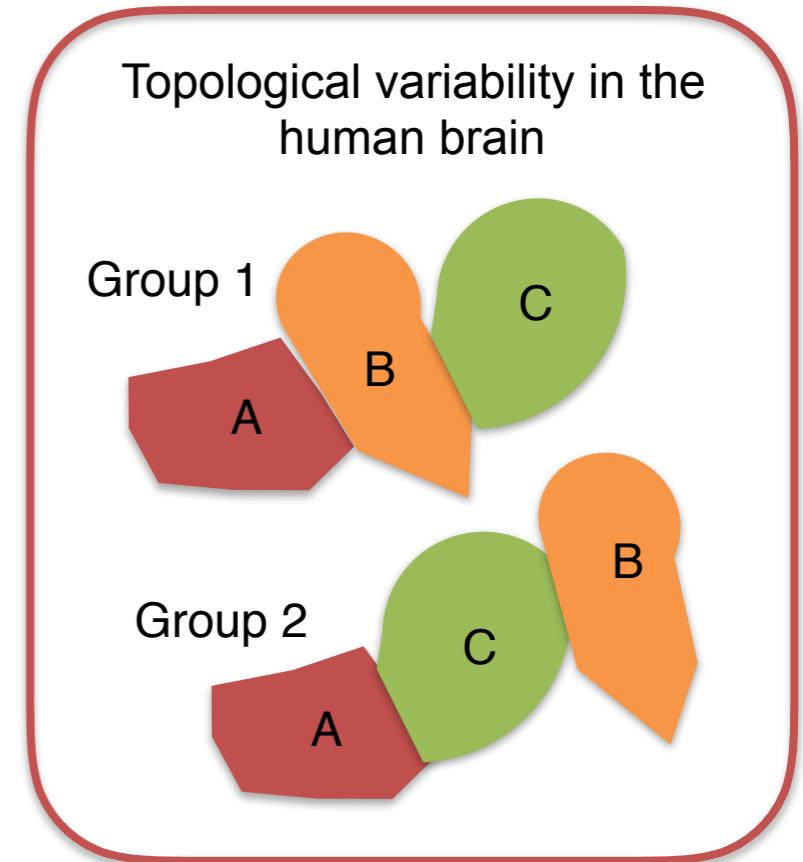
- (Functional Connectivity) Graph convolutions
Ktena
- Joshi, Anand A., et al. "Predicting cognitive scores from resting fMRI data and geometric features of the brain." *Medical Imaging 2019: Image Processing*. Vol. 10949. International Society for Optics and Photonics, 2019.
- Sabuncu recent paper

What is really driving predictions?

- Are changes really due to changes in functional connectivity strength
- Or are they due to changes in functional brain organisation (topology)
- Note this is true whether functional data is used or not

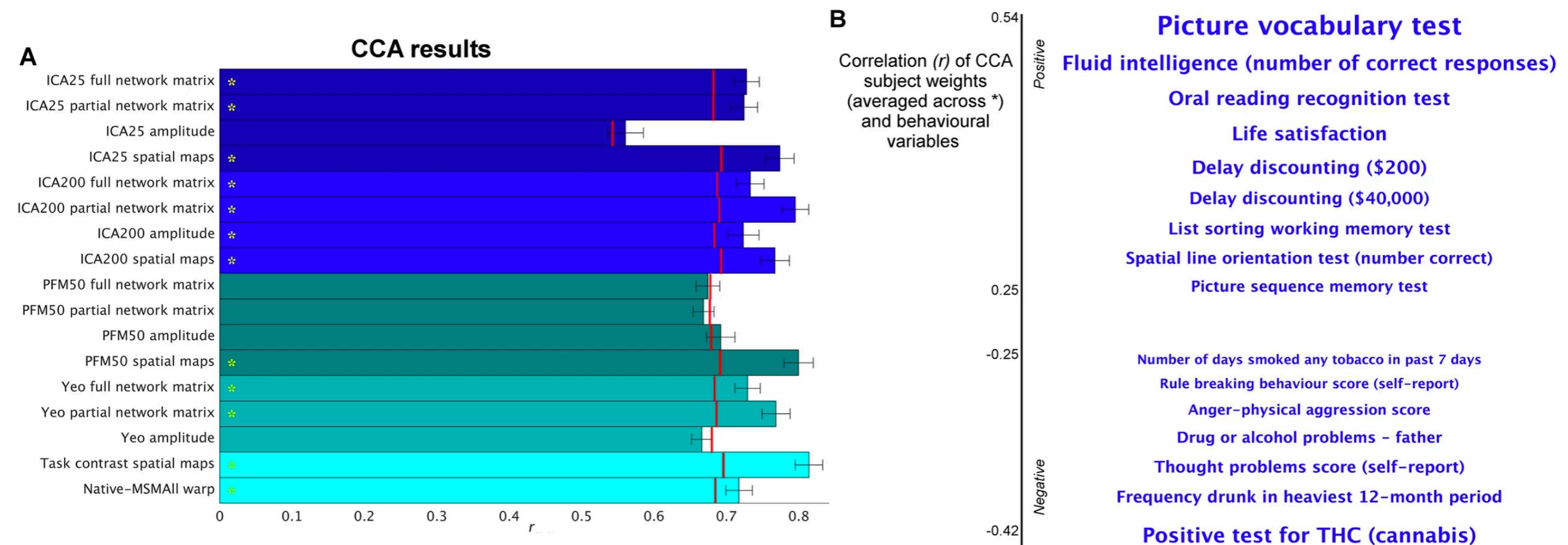
What is really driving predictions?

- Are changes really due to changes in functional connectivity strength
- Or are they due to changes in functional brain organisation (topology)
- Note this is true whether functional data is used or not



The relationship between spatial configuration and functional connectivity of brain regions

- Doing CCA with rfMRI spatial maps is as (if not more predictive) of behaviour than using functional connectivity matrices

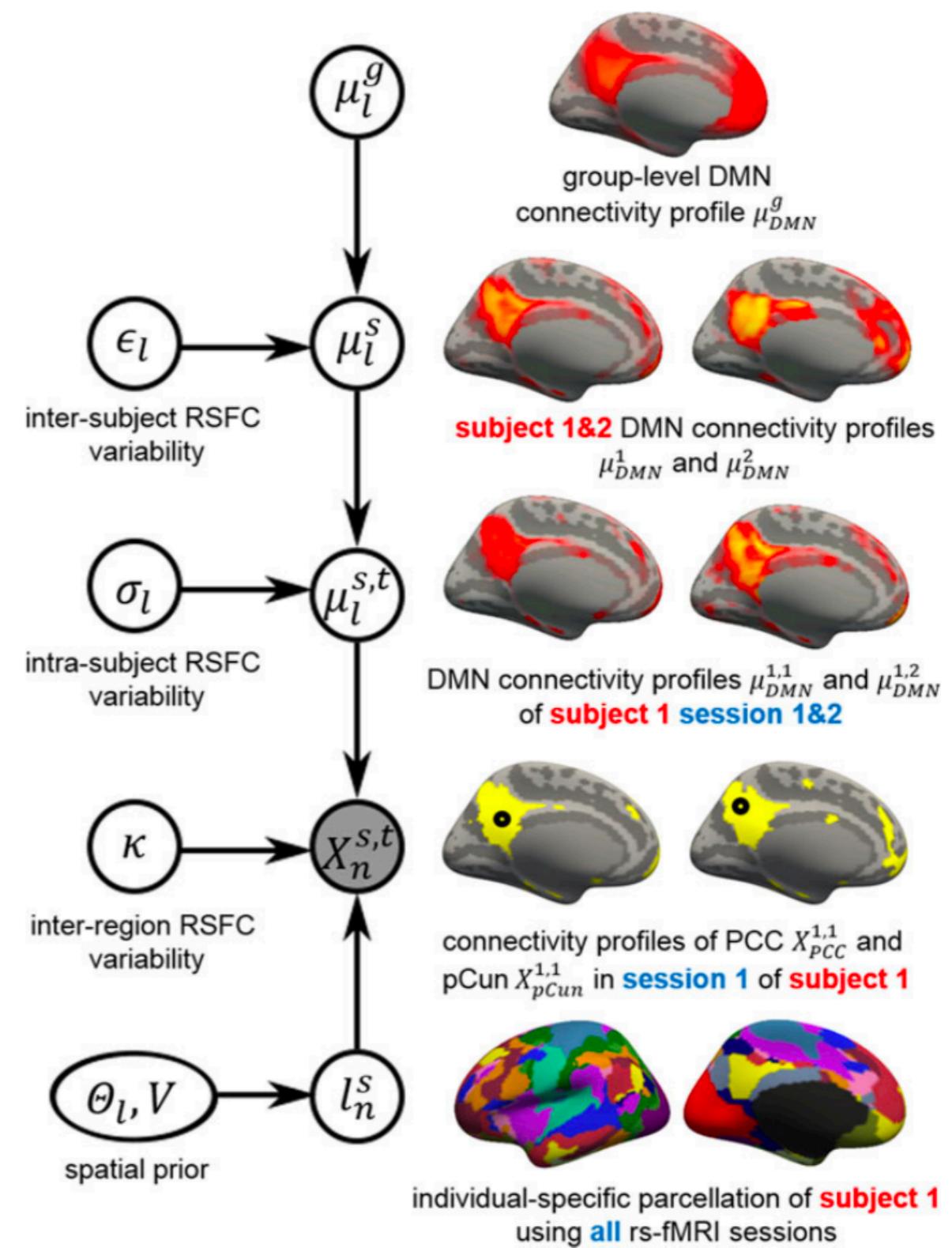


* This will also apply to structural connectivity

Bijsterbosch, Janine Diane, et al. "The relationship between spatial configuration and functional connectivity of brain regions." Elife

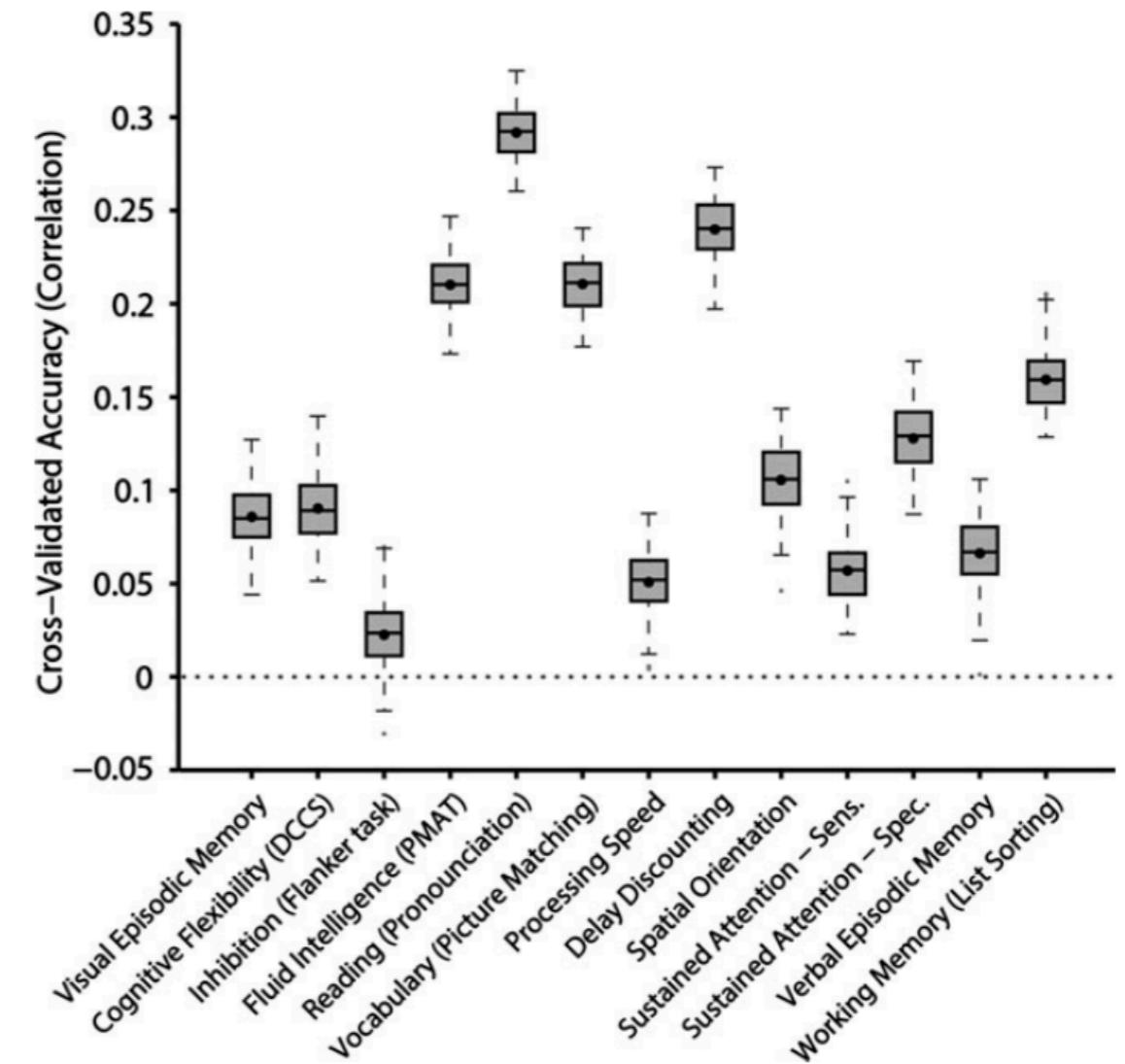
Spatial Topography of Individual-Specific Cortical Networks Predicts Human Cognition, Personality, and Emotion

- Similar finding
- Spatial maps derived from bayesian modelling of subject-specific functional organisation
- More predictive of behaviour than static atlases



Spatial Topography of Individual-Specific Cortical Networks Predicts Human Cognition, Personality, and Emotion

- Similar finding
- Spatial maps derived from bayesian modelling of subject-specific functional organisation
- More predictive of behaviour than static atlases

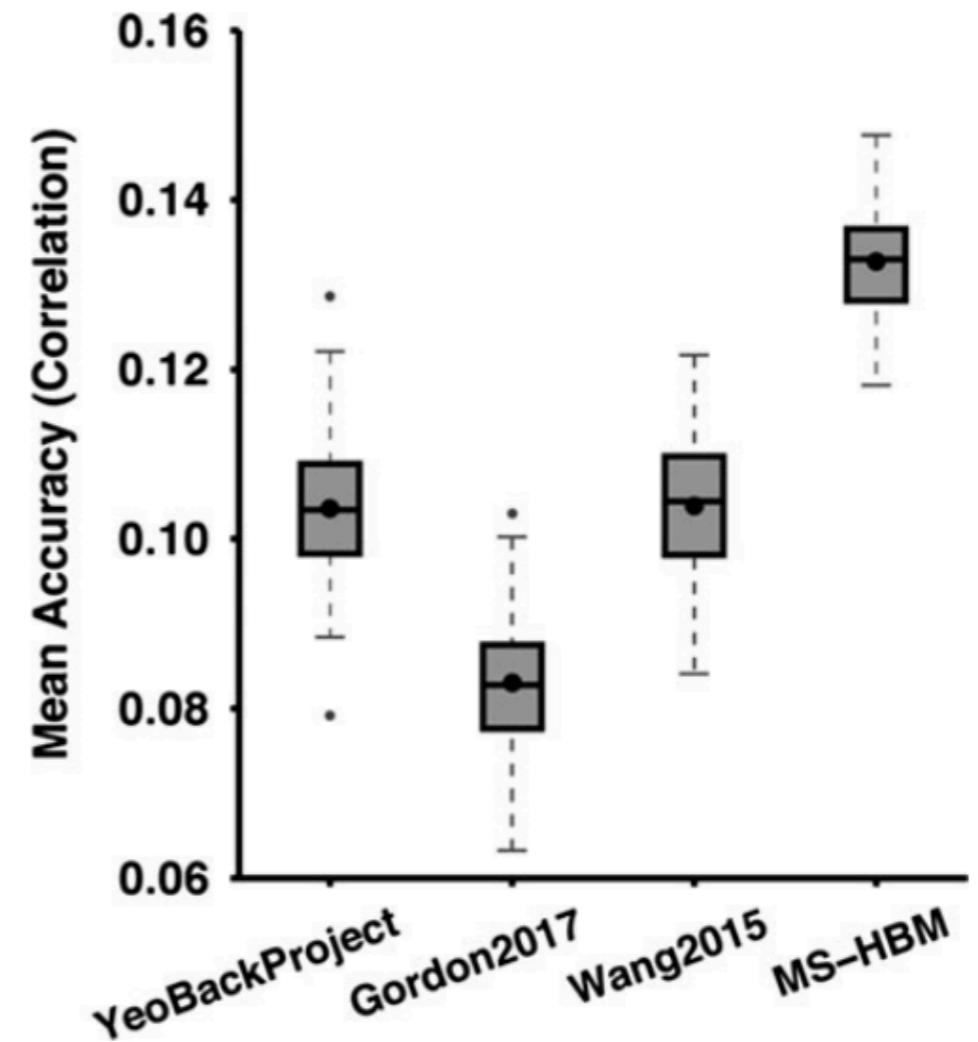


Spatial Topography of Individual-Specific Cortical Networks Predicts Human Cognition, Personality, and Emotion

- Similar finding
- Spatial maps derived from bayesian modelling of subject-specific functional organisation
- More predictive of behaviour than static atlases

Spatial Topography of Individual-Specific Cortical Networks Predicts Human Cognition, Personality, and Emotion

- Similar finding
- Spatial maps derived from bayesian modelling of subject-specific functional organisation
- More predictive of behaviour than static atlases



Why is this important

- Difficulties in interpretation of ML predictions
- Requires rethinking of whole pre-processing pipeline

Should we be doing DL on functional/structural connectivity

- Aside from interpretability problem
- He, Tong, et al. "Do Deep Neural Networks Outperform Kernel Regression for Functional Connectivity Prediction of Behavior?." *BioRxiv* (2018): 473603.
- Compared the performance of three DNN architectures and a classical machine learning algorithm (kernel regression) in predicting individual phenotypes from whole-brain resting-state functional connectivity (RSFC) patterns.
 - Fully connected
 - BrainNet CNN
 - Graph convolutional neural network (GCNN)
- DNNs do not outperform kernel regression across a wide range of behavioral and demographic measures

Should we be doing DL on functional/ structural connectivity

Model	Sex	Age		Pairs matching	Fluid intelligence
	Accuracy	Correlation	MAE	Correlation	Correlation
Kernel Regression	0.916	0.600	4.826	0.061	0.239
FNN	0.908	0.598	4.896	-0.0006	0.239
BrainNetCNN	0.917	0.596	4.836	0.063	0.236
GCNN	0.908	0.577	5.110*	0.030	0.155*

Table 1. Prediction performance of four behavioral and demographic measures in the UK Biobank. For age (MAE), lower values imply better performance. For all the other measures, larger values imply better performance. **Bold** indicates best performance, although it does not imply statistical significance. Statistical tests were performed to compare kernel regression with each of the three DNNs. * indicates statistical significance after FDR ($q < 0.05$) correction.

Should we be doing DL on functional/ structural connectivity

