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Imaging biomarkers of neural circuits in normal development and disease

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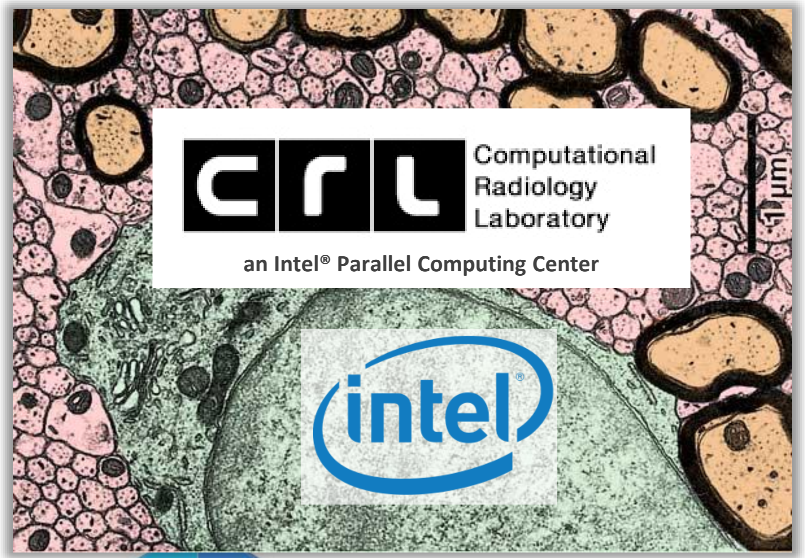


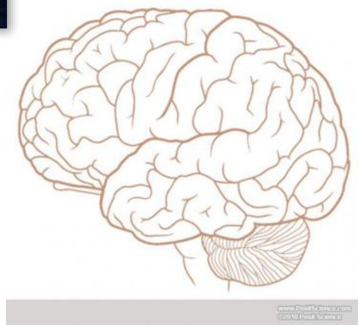
Harvard Medical School

intel AI

Concussion

Multiple Sclerosis

National Multiple Sclerosis Society



Today's *in vivo* imaging tools to assess the brain are limited

Autism Spectrum Disorder

Normal brain development

Cost of mental illness: ~$317 billion per year (Insel 2008)

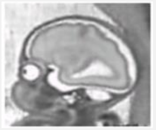
Traditional (historical) approach in Neurology		What we should do
Focus on symptoms	⟺	Focus on the underlying neural basis of the disorder.
Diagnose patients on the effect of the disconnections	⟺	Diagnose patients based on the location of the disconnections.

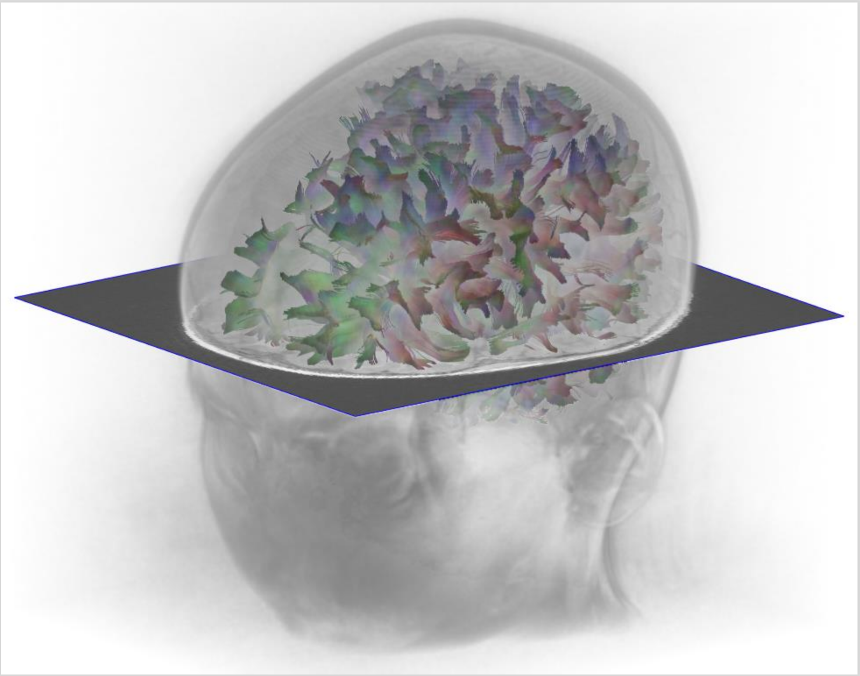
Concussion

Multiple Sclerosis

Autism Spectrum Disorder

Normal brain development





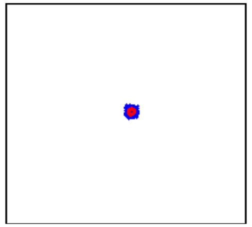
- Concussion, MS, ASD:
  Disconnection syndromes (?)
- Need to assess the microstructural integrity of brain connections
  Axonal loss? Inflammation? Demyelination? Remyelination?
  Atypical wiring of the brain?

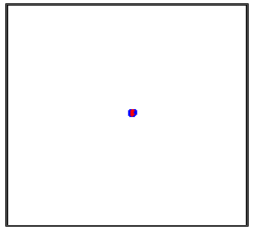
Need to characterize neural circuits

TECHOLOGY

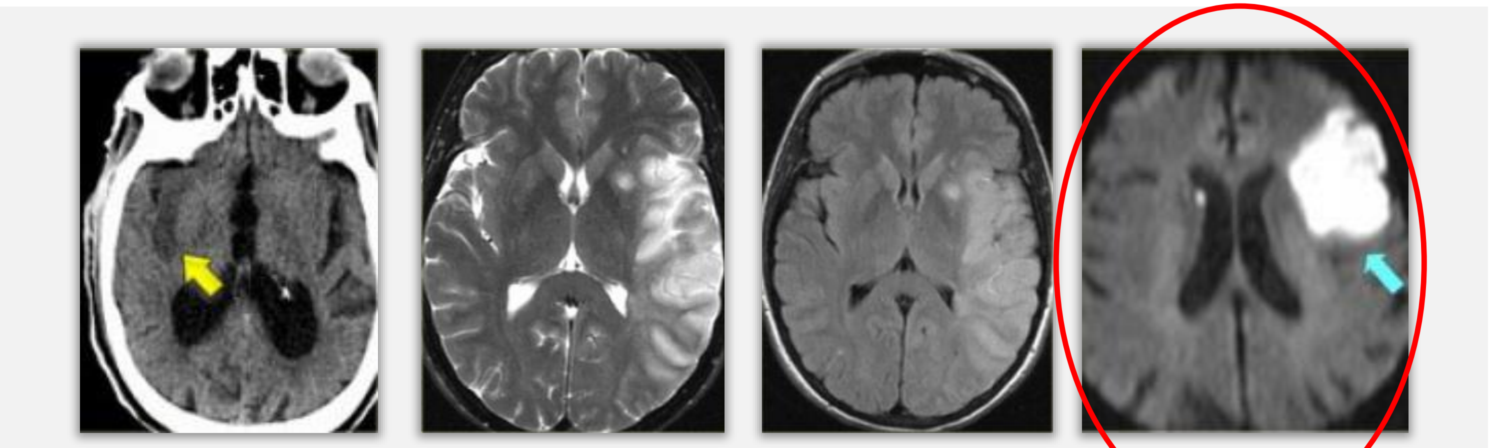
Diffusion-weighted Imaging (DWI)

Assessment of the restrictions and hindrances to water diffusion in biological tissues


Free diffusion

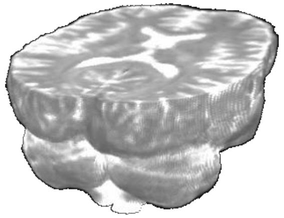

Restricted diffusion

Originally developed for assessing strokes


CT | MRI-PD | MRI-T2 | DWI

TECHNOLOGY

Diffusion-weighted Imaging



Each image: 3-D

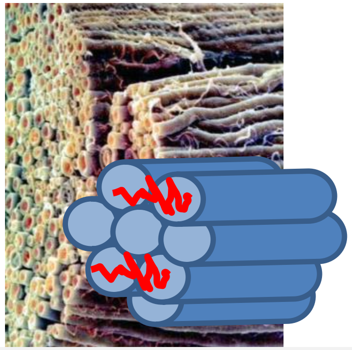
2nd Generation DWI

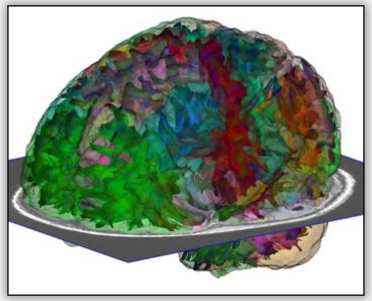
Assessment of the 4-D diffusion in each pixel

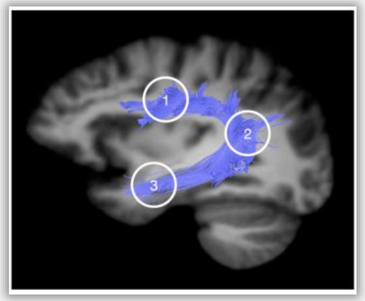
- Varying diffusion orientations
- Varying diffusion length scales

} Large amount of data

⇨ Provides *in vivo* insight into the architecture and microstructure of neural circuits (the “wires” of the brain)

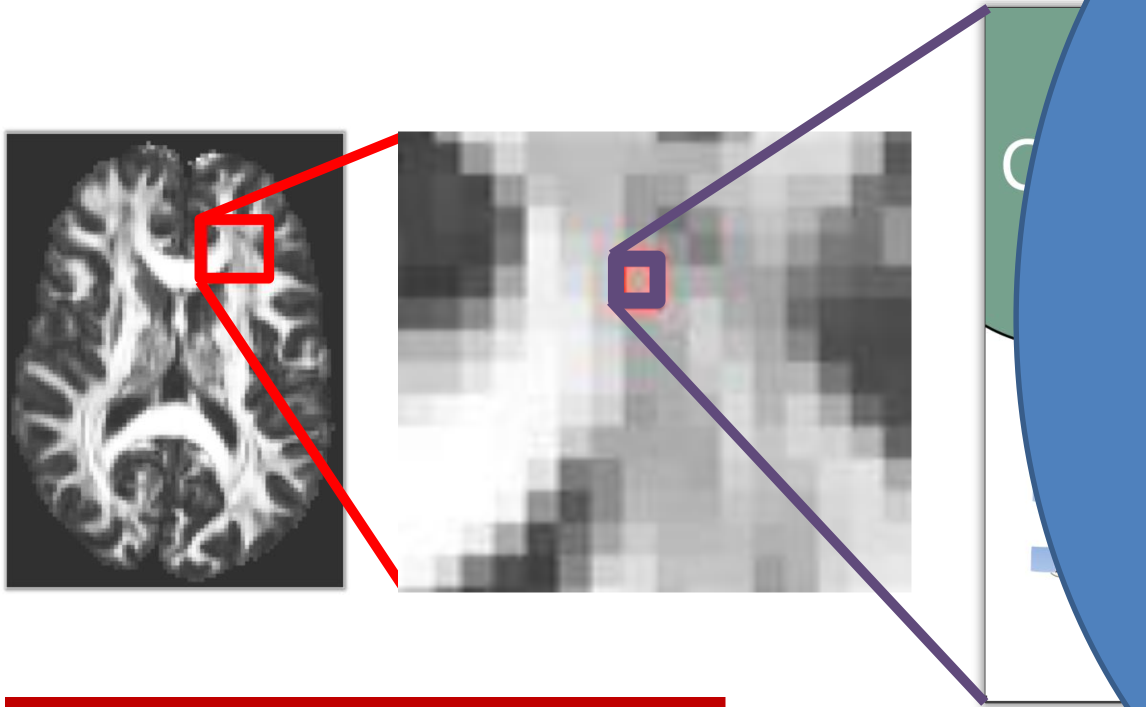






Diffusion tensor imaging (DTI)

Over-simplified summary of the diffusion in voxels



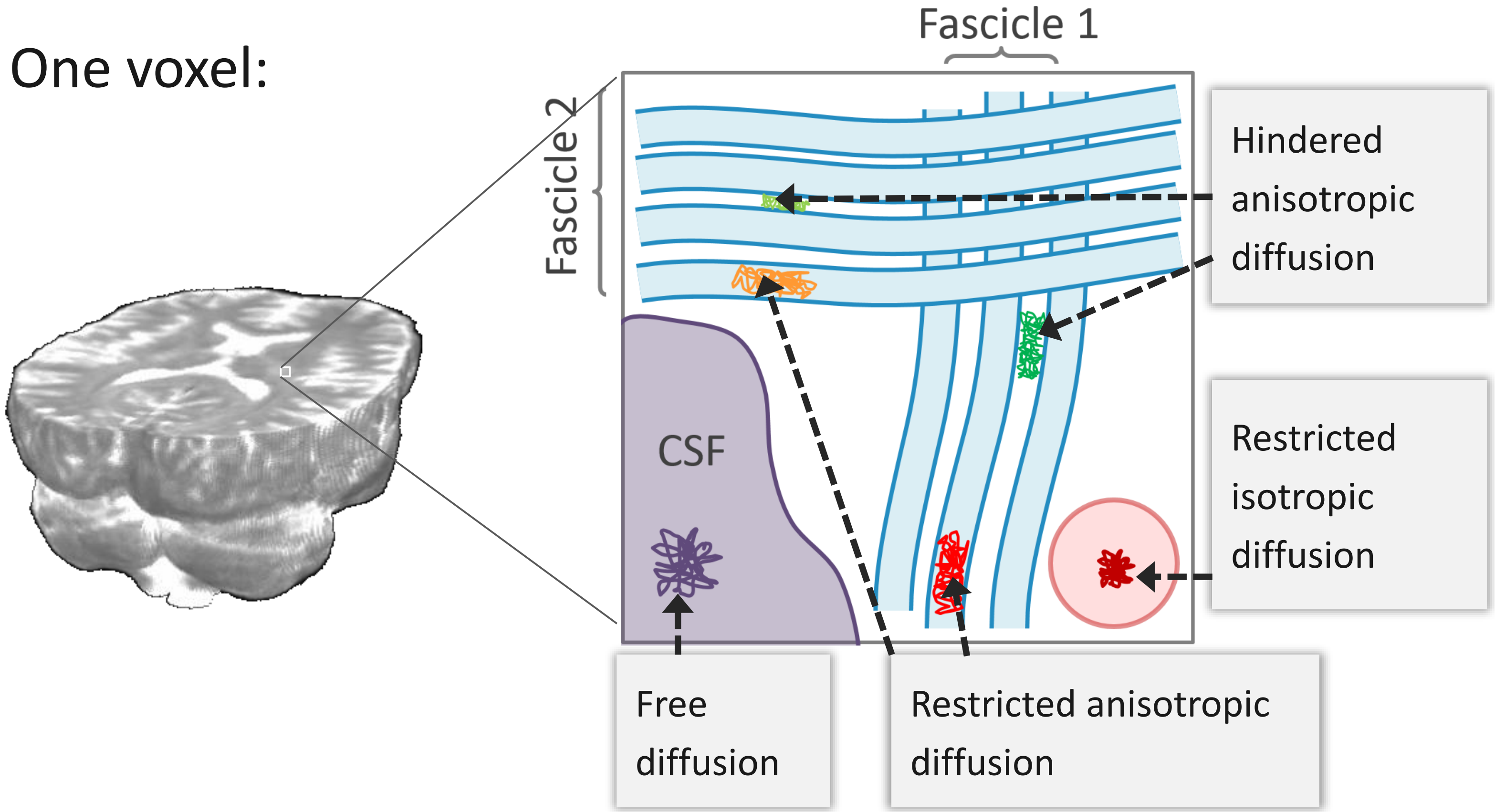
Tensor

Limited information

TECHOLOGY

Scientific Contribution: Diffusion Compartment Imaging (DCI)

One voxel:



Disentangle the various types of diffusion within voxel
=> Non invasive characterization of properties of neural circuits

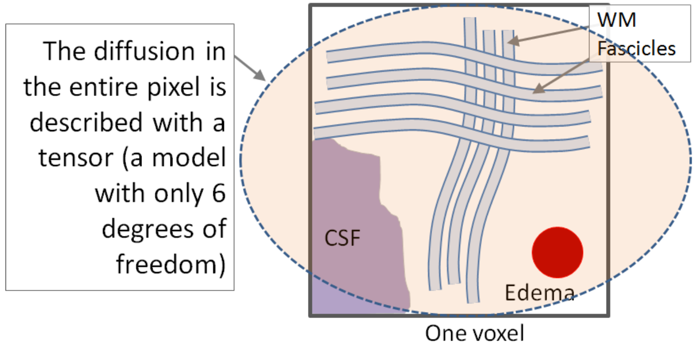
TECHNOLOGY

Diffusion-weighted Imaging

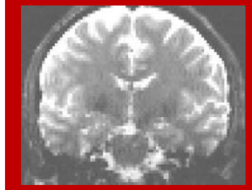
We have developed a novel diffusion-weighted imaging technique

Conventional technique

Diffusion Tensor Imaging (DTI)



Summarizes the diffusion with an oversimplified model

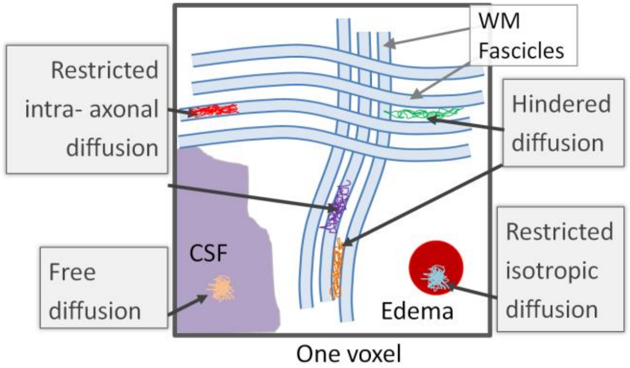


Characterizes each pixel of the 3-D image of the brain

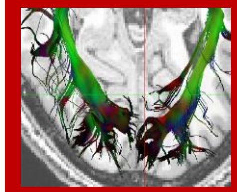
Limited information

Scientific contribution

Diffusion Compartment Imaging (DCI)



Description of each type of diffusion in each 3-D pixel



Characterizes properties of each neural circuit

Highly specific information

(Some mathematics…)

$$S(\mathbf{g}, b) = \sum_{j=1}^{N_c} S_0 \int_{\mathbf{D}\in\mathrm{Sym}^+(3)} P_j(\mathbf{D}) \exp\left(-b\mathbf{g}^T\mathbf{D}\mathbf{g}\right) d\mathbf{D}$$

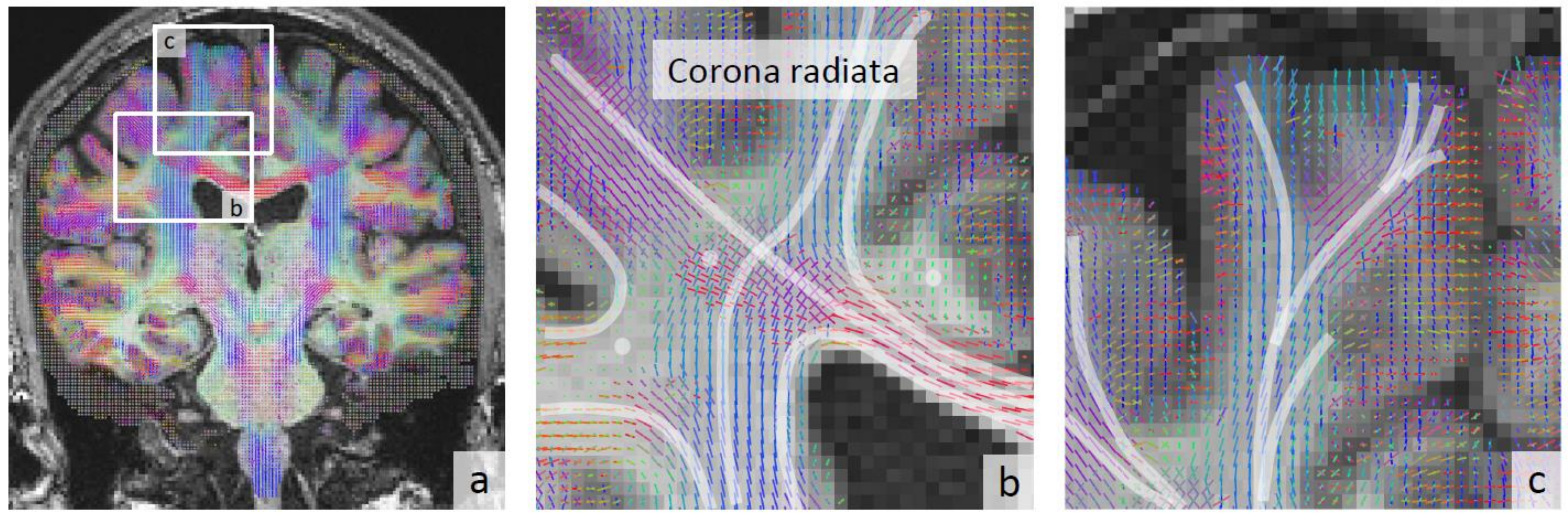
$$P(\mathbf{D}; \kappa, \mathbf{\Psi}, \mathbf{\Theta}) = \frac{[\det(\mathbf{D})]^{\kappa-2}}{[\det(\mathbf{\Psi})]^{\kappa}\Gamma_3(\kappa)} \exp[-\mathrm{tr}(-\mathbf{\Theta} - \mathbf{\Psi}^{-1}\mathbf{D})] F_{0,1}(\kappa; \mathbf{\Theta}\mathbf{\Psi}^{-1}\mathbf{D})$$

$$S = S_0 \sum_{j=1}^{N_c} \left(1 + b\mathbf{g}^T\mathbf{\Psi}_j\mathbf{g}\right)^{-\kappa_j} \exp\left(-\frac{b\mathbf{g}^T\mathbf{\Psi}_j\mathbf{\Theta}_j\mathbf{g}}{1 + b\mathbf{g}^T\mathbf{\Psi}_j\mathbf{g}}\right)$$

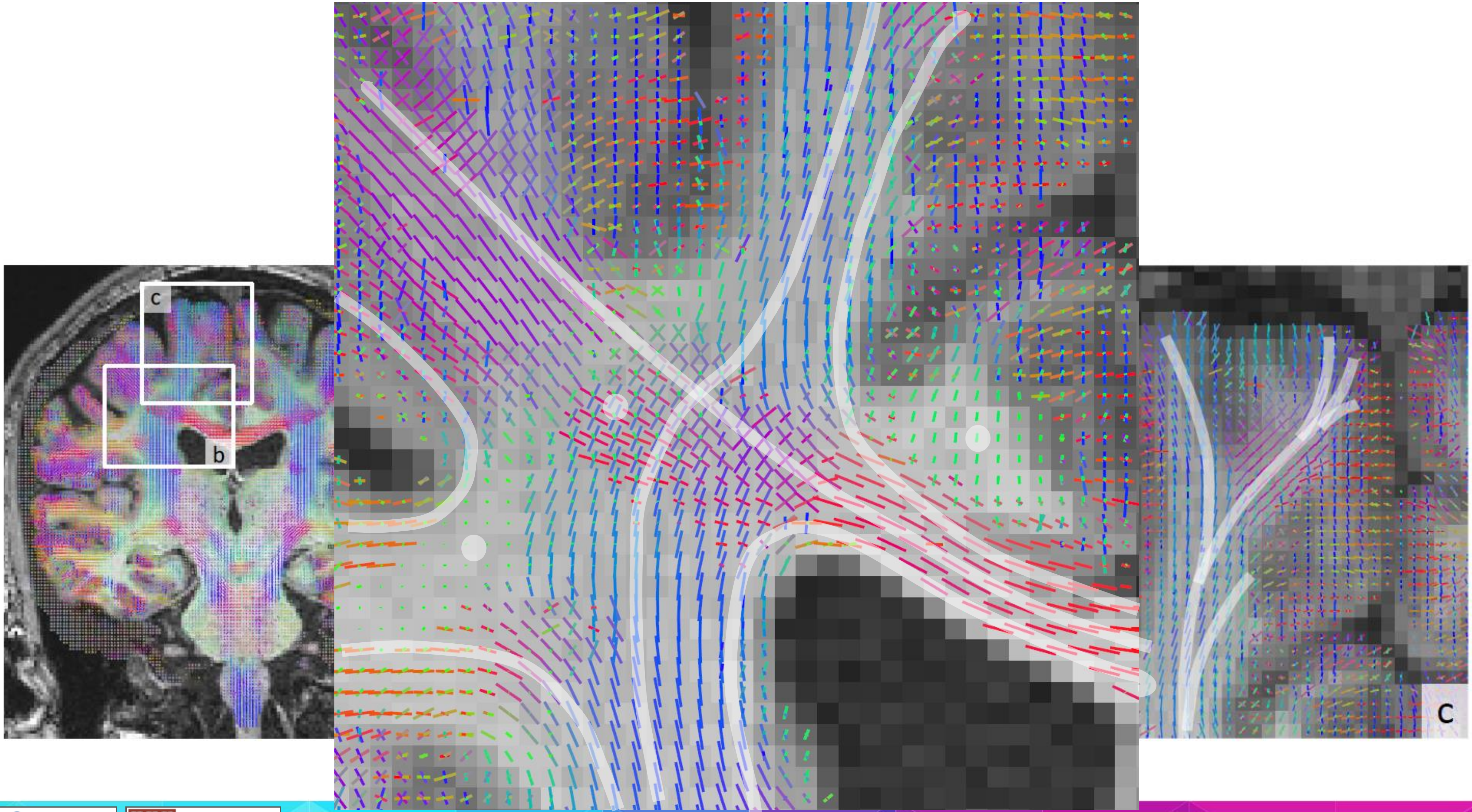
$$S(\mathbf{g}, b) = S_0\left[f_{\mathrm{iso}}\exp(-bD_{\mathrm{iso}}) + \sum_{j=1}^{N_f} f_j \left(1 + b\mathbf{g}^T\mathbf{D}_{0,j}\left(\kappa_j \mathrm{I}_3 + \mathbf{\Theta}_j\right)^{-1}\mathbf{g}\right)^{-\kappa_j} \exp\left(-\frac{b\mathbf{g}^T\mathbf{D}_{0,j}\left(\kappa_j \mathrm{I}_3 + \mathbf{\Theta}_j\right)^{-1}\mathbf{\Theta}_j\mathbf{g}}{1 + b\mathbf{g}^T\mathbf{D}_{0,j}\left(\kappa_j \mathrm{I}_3 + \mathbf{\Theta}_j\right)^{-1}\mathbf{g}}\right)\right]$$

Diffusion Compartment Imaging (Healthy Subject)

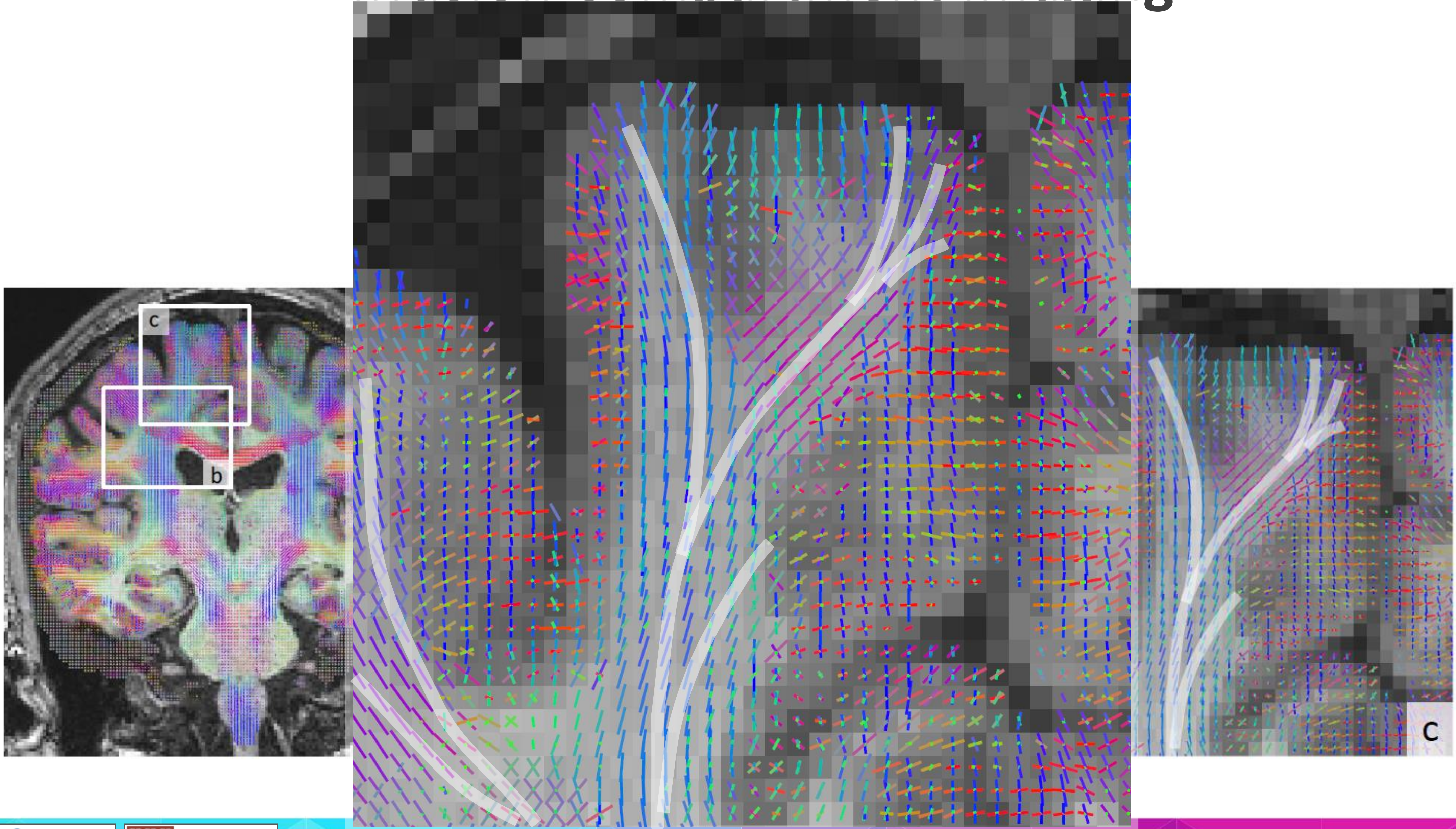
Unprecedented characterization of neural circuits



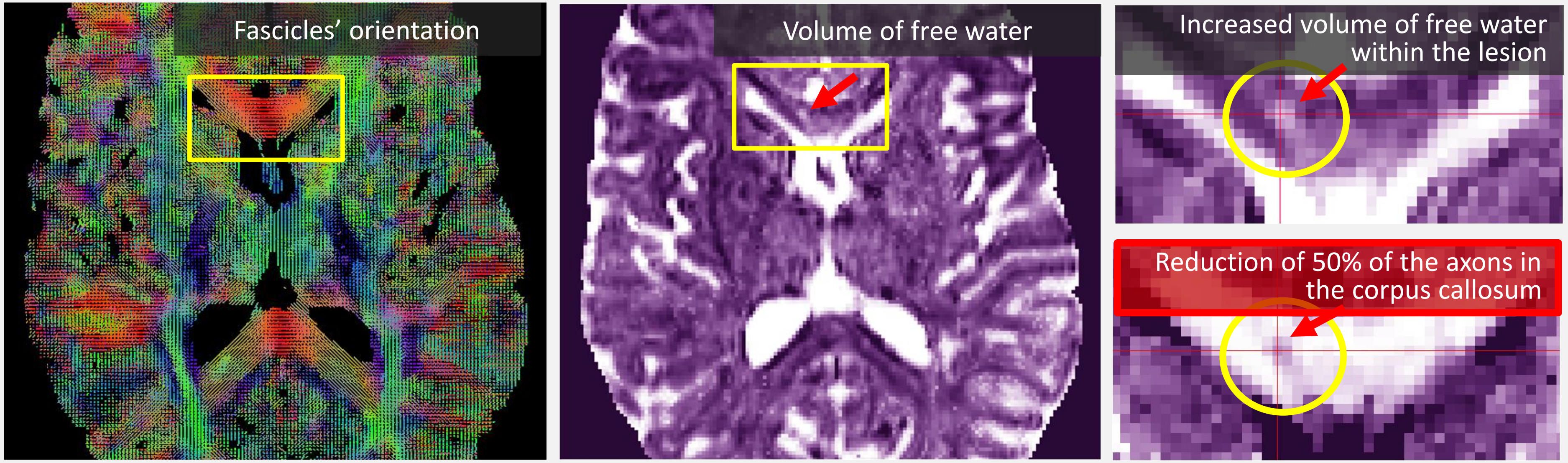
Diffusion Compartment Imaging

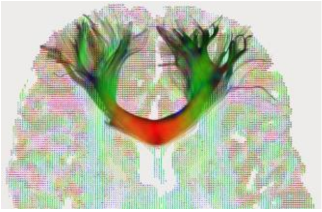


Diffusion Compartment Imaging



Diffusion Compartment Imaging
in Concussion





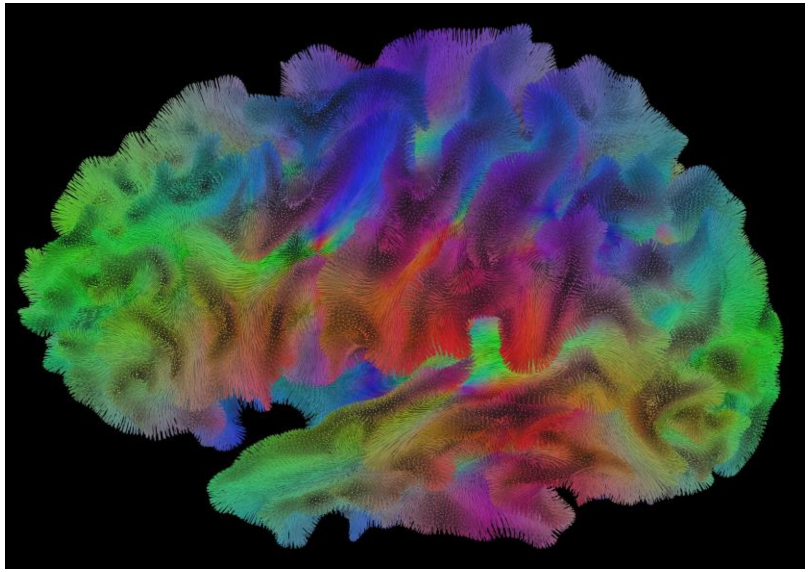
⇨ Suggest diffuse axonal injury leading to axonal death, while the remaining axons remain unchanged

But…

Originally a few days of computations for each case…

The Computational Radiology Laboratory at Boston Children's Hospital,

An intel Parallel Computing Center



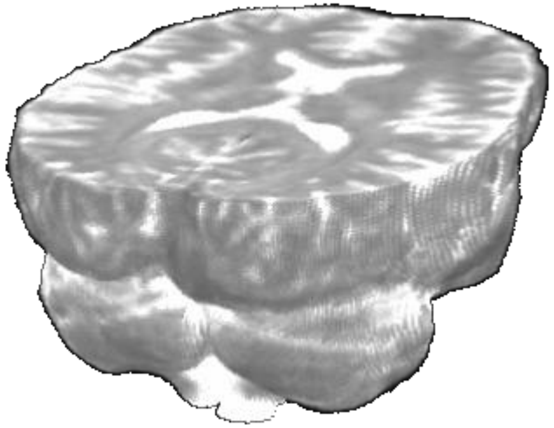
Technical goals:

- Improve cache performance, vectorization performance and multi-threading performance for Intel® Xeon® processors
- Improved data structures
- Improved algorithms
- Open source implementations

⇨ Modernize medical image computing

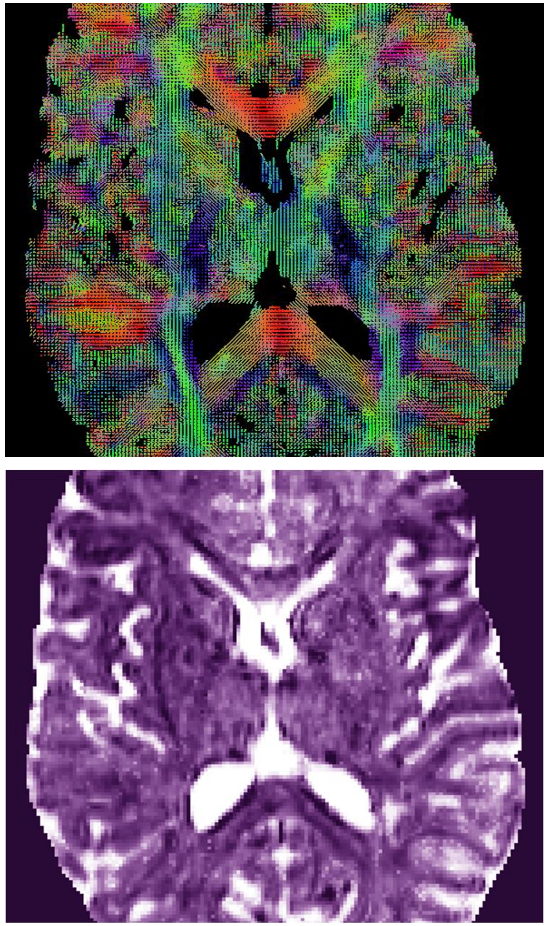
Programming environment

Diffusion Compartment
Imaging Estimation

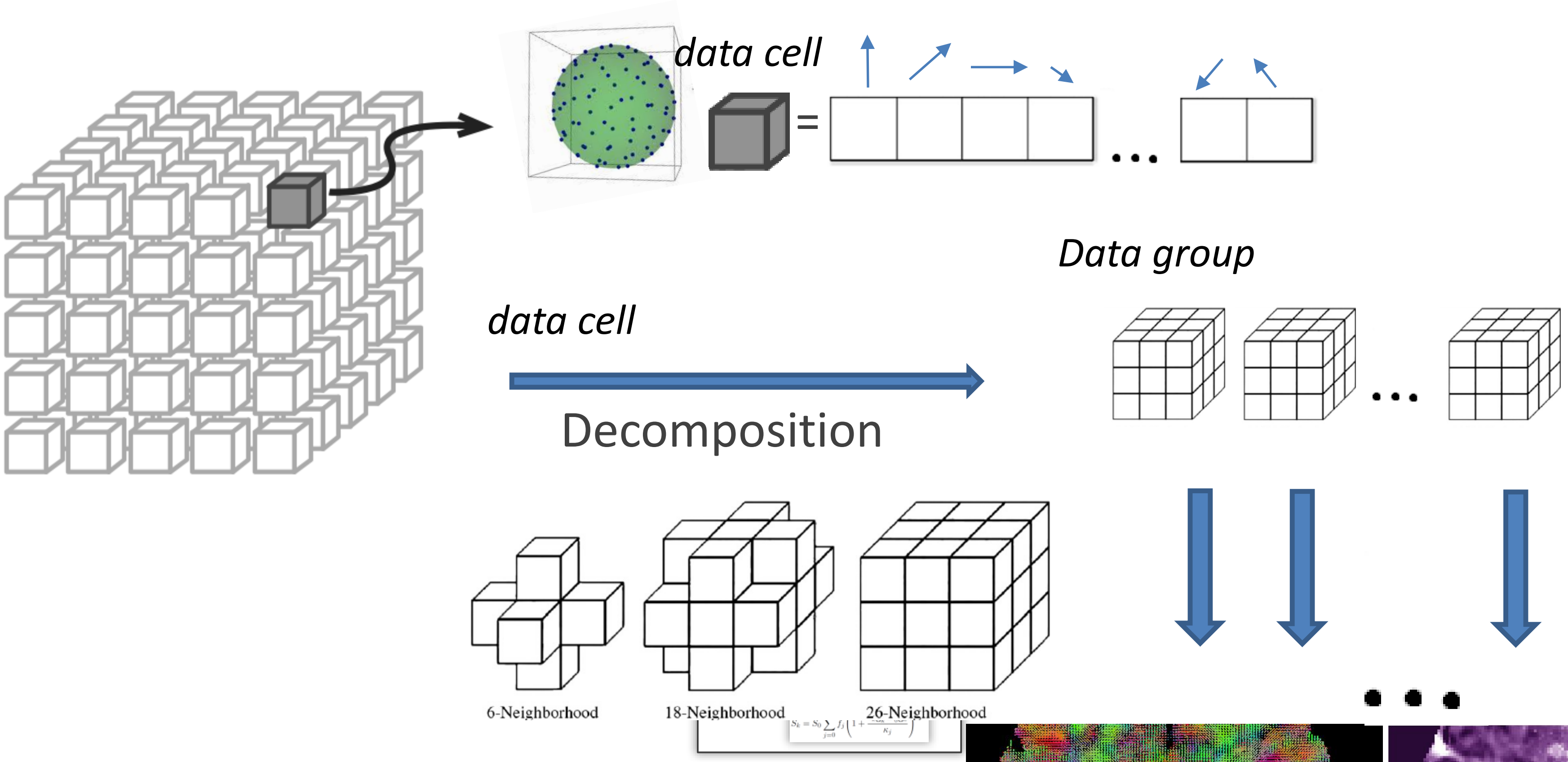


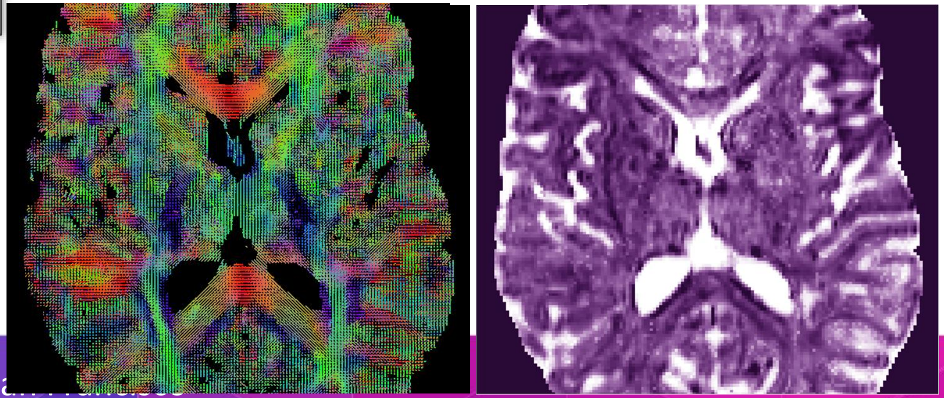
Large 4-D dataset
for each patient

Filter



Programming environment





Improvements

Diffusion Compartment Imaging Estimation

Intel® Xeon(R) CPU E5-2697 v2 @ 2.70GHz × 24 core, 2 sockets, image 2x2x2mm^3

- Single core: 43h06m21s — x14.2
- Parallelization v1: 03h02m02s — x1.76
- Memory optimization: 01h43m31s — x1.12
- Vectorization: 01h32m38s — x1.37
- TBB filter, dynamic pool: 01h07m26s — x1.22
- Flexible TBB decomposition: 55m23s — x1.44
- Optimizer improvement: 38m27s — x1.12
- Intel compilation flag: 34m14s — x1.4

X7.4

x105

- **Intel® Xeon Platinum™ 8160** 23m53s
  (Skylake 8160, 24 cores, 2.1Ghz nominal, 2 sockets)

Scalability

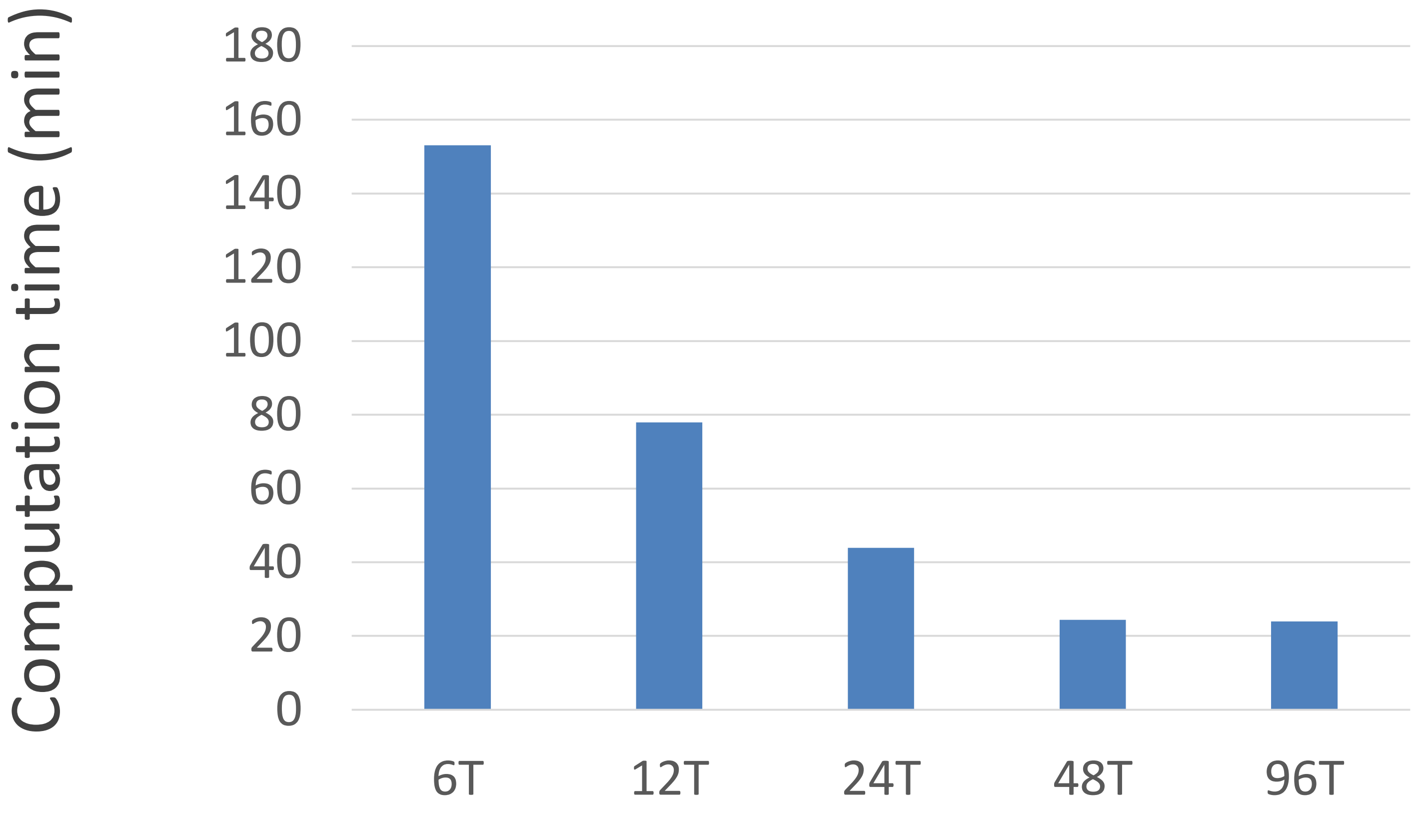


Image Resolution: $2x2x2mm^3$

Intel® Xeon Platinum™ 8160 Skylake, 24 cores, 2 sockets, Stampede2, TACC – Texas Advanced Computing Center

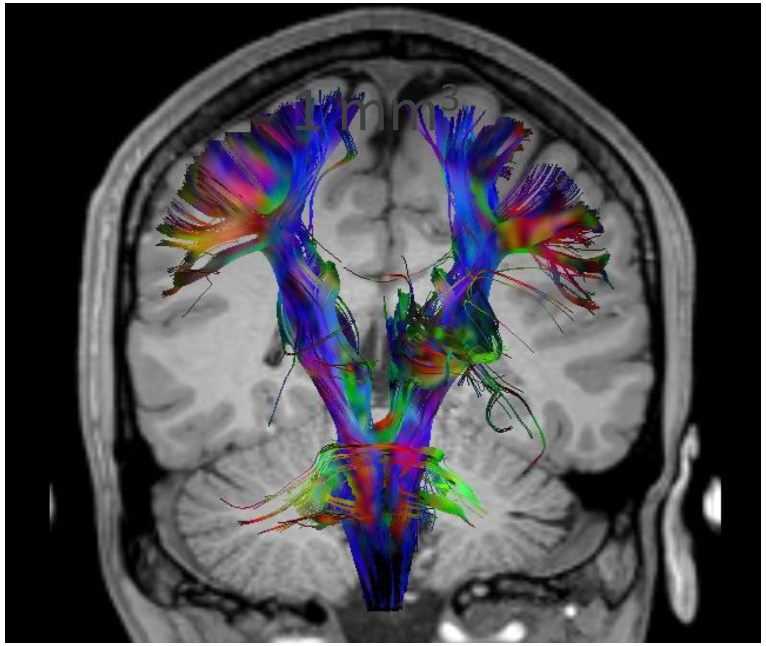
The resolution of images is increasing

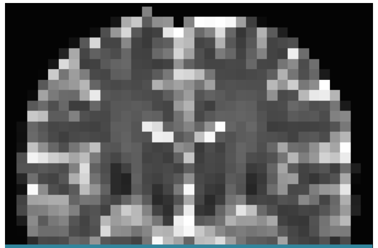
- Benchmarking done with conventional 8 mm^3 voxel images (128x128x71 voxels)
- We can see more structure with voxel images (256x256x142 voxels)

→ Processing times:

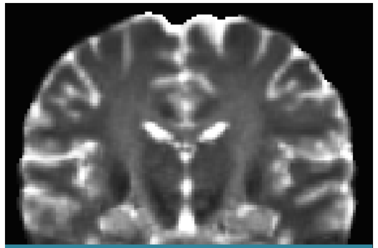
Single core version on Intel® Xeon® : (>14d)	344h50m
Parallelization v1 on Intel® Xeon® :	24h16m (1d)
Other improvements on Intel® Xeon® :	4h33m
Intel® Xeon Platinum™ 8160 :	2h32m

x150





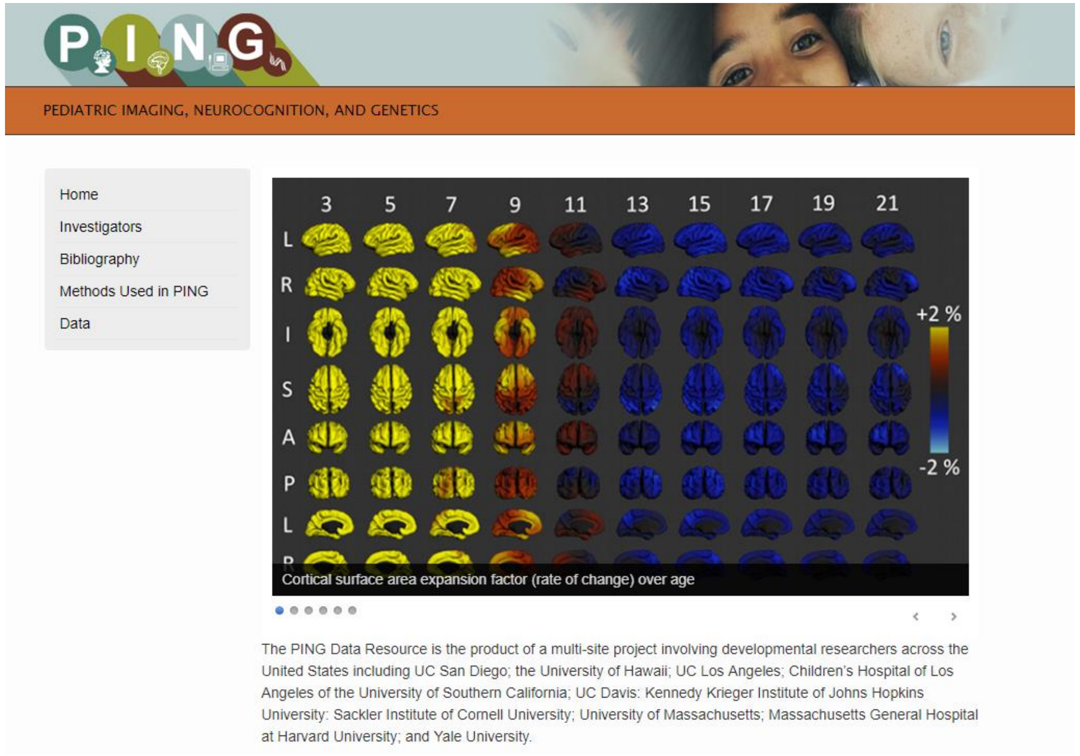
$4x4x4mm^3$



$1x1x1mm^3$

Allows large scale processing

Pediatric Imaging, Neurocognition and Genetics (PING) dataset



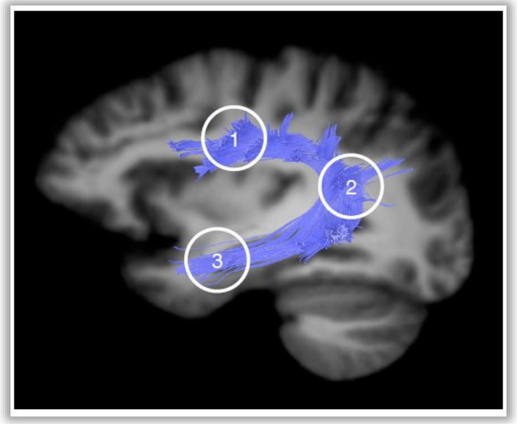
- 698 scans from the PING database
  - Single shell HARDI DWI with a prior
- Computation at the National Energy Research Scientific Computing Center (NERSC) Haswell and Ivy Bridge nodes
- Real processing time spent:
  328 days
- Single processor equivalent time (from system's ticks) :
  6504 days, ~ 17.8 years!

Transforming the Practice of Radiology

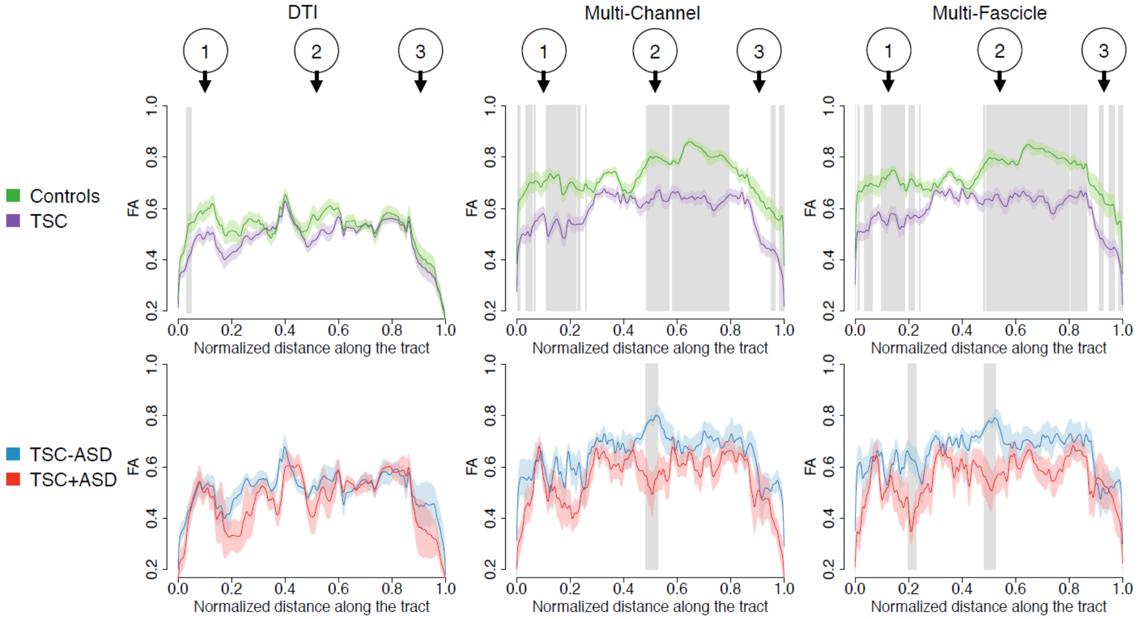
Quantitative Cohort Comparison

Big data analysis

- Brain microstructure characterization in ASD



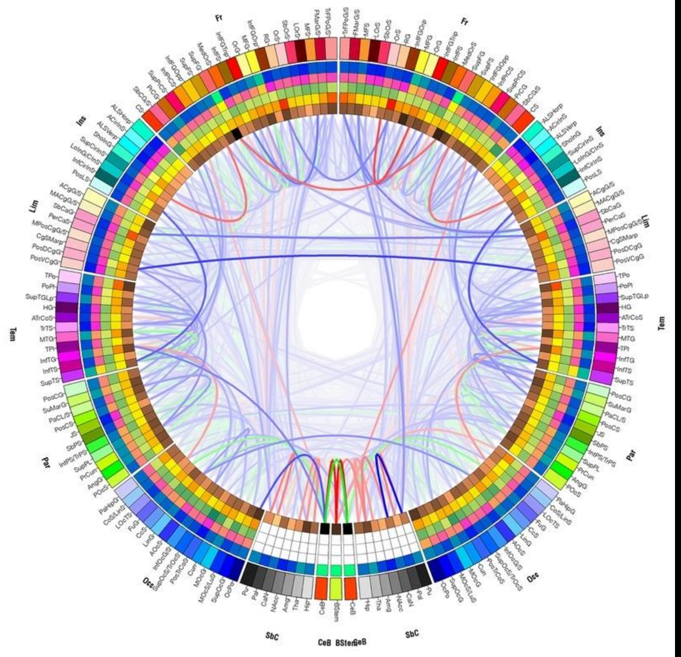
[Taquet et al., 2014]

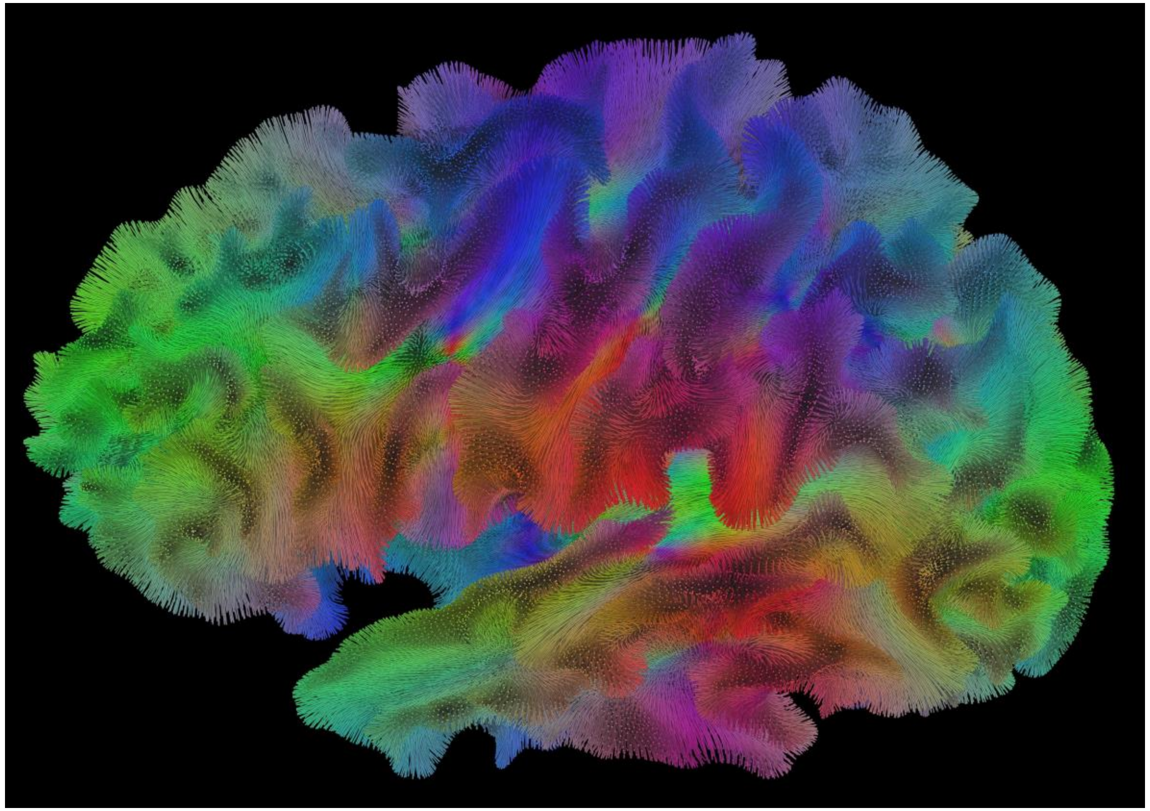


Understanding Neural Circuits

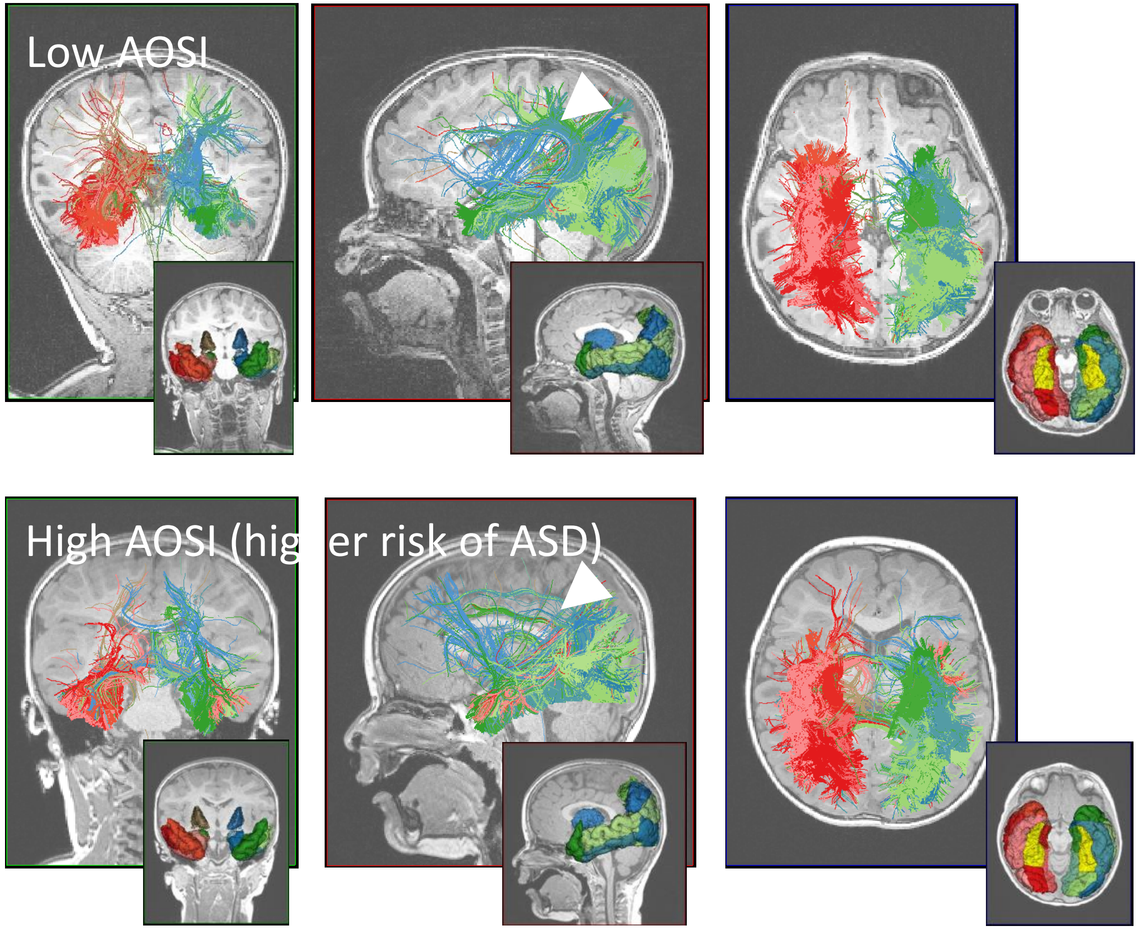
Human Connectome Project (HCP)

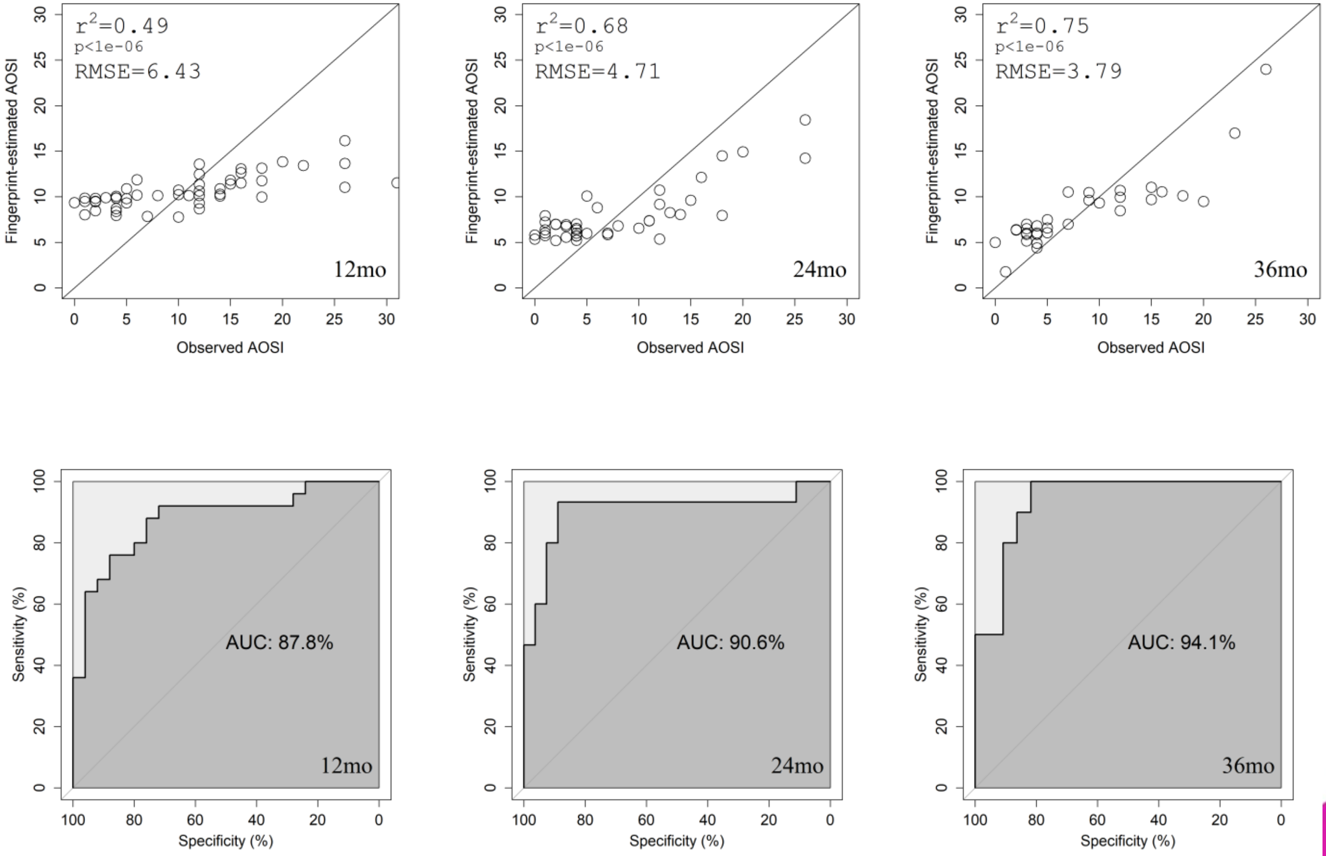
- Mapping the structural and functional connections



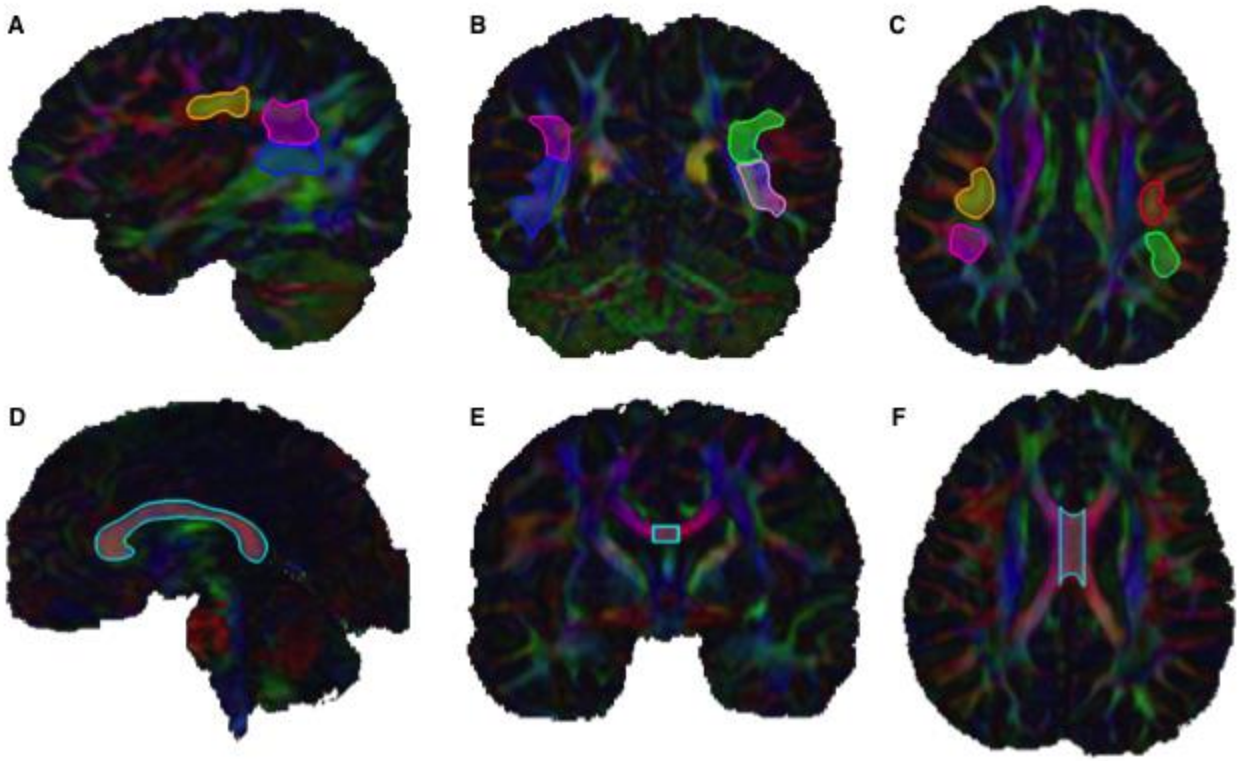


Connectivity fingerprint of the fusiform gyrus in Autism





White matter maturation in Autism



a. Prediction of dichotomized AOSI from DTI metrics of white matter ROI and log age in the ≤ 12 months of age subsample.

ROI	DTI metric	Sensitivity	Specificity	PPV	NPV	AUC	95% CI
R Wernicke	MD	66.67	86.36	72.73	82.61	76.14	58.42 - 93.86
L Wernicke	FA	83.33	63.64	55.56	87.50	75.76	58.33 - 93.18
R Geschwind	FA	83.33	63.64	55.56	87.50	74.24	57.26 - 91.22
L Geschwind	MD	66.67	77.27	61.54	80.95	73.11	55.18 - 91.03
R Geschwind	MD	58.33	86.36	70.00	79.17	71.21	52.31 - 90.11
R Wernicke	FA	75.00	68.18	56.25	83.33	70.83	52.68 - 88.98

b. Prediction of dichotomized AOSI from DTI metrics of white matter ROI, log age, and repeated measures in the longitudinal subsample.

ROI	DTI metric	Sensitivity	Specificity	PPV	NPV	AUC	95% CI
L Geschwind	FA	86.67	80.00	72.22	90.91	87.20	75.88 - 98.52
L Wernicke	FA	86.67	76.00	68.42	90.48	85.07	73.34 - 96.79
L Broca	FA	93.33	52.00	53.85	92.86	77.33	62.49 - 92.17
R Geschwind	FA	60.00	88.00	75.00	78.57	76.53	61.26 - 91.80
R Wernicke	FA	86.67	60.00	56.52	88.24	75.47	60.52 - 90.42
L Broca	MD	80.00	60.00	54.55	83.33	71.47	55.26 - 87.67
R Wernicke	MD	86.67	44.00	48.15	84.62	71.47	55.00 - 87.94
L Geschwind	MD	73.33	72.00	61.11	81.82	70.67	54.09 - 87.25
R Geschwind	MD	60.00	76.00	60.00	76.00	70.67	54.35 - 86.98
L Wernicke	MD	60.00	84.00	69.23	77.78	70.13	52.85 - 87.42

ROI with AUC > 70.00 shown. Longitudinal Sample, N=40 ; ≤ 12 months of age subsample, N=34.

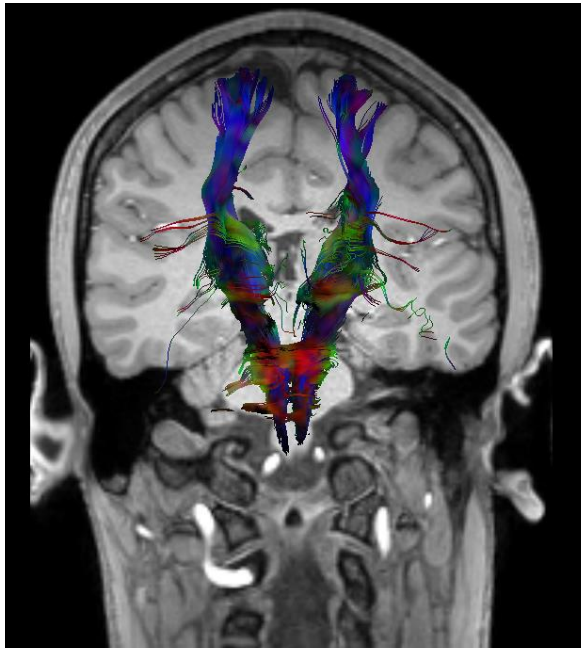
AOSI= Autism Observation Scale for Infants; AF= Arcuate Fasciculus; AUC= Area Under Curve; CI=Confidence Interval; DTI= Diffusion Tensor Imaging; FA=Fractional Anisotropy X 10; L=left; MD=Mean Diffusivity mm^2/s X 10^3; NPV=Negative Predictive Value; PPV= Positive Predictive Value; R=right; ROI=Region of Interest.

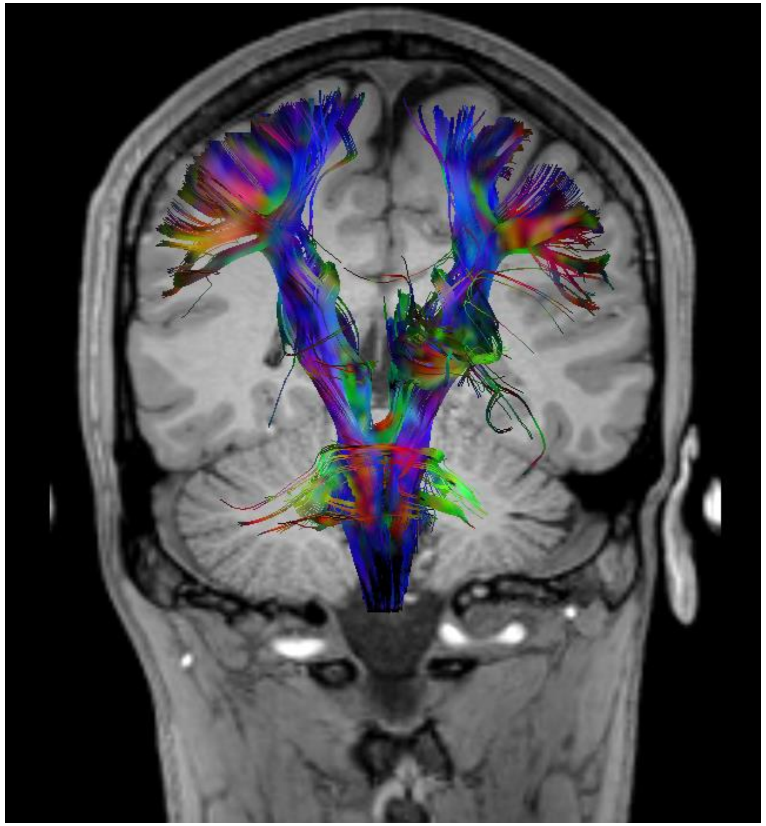
Neural Circuitry in the Individual

Surgical planning

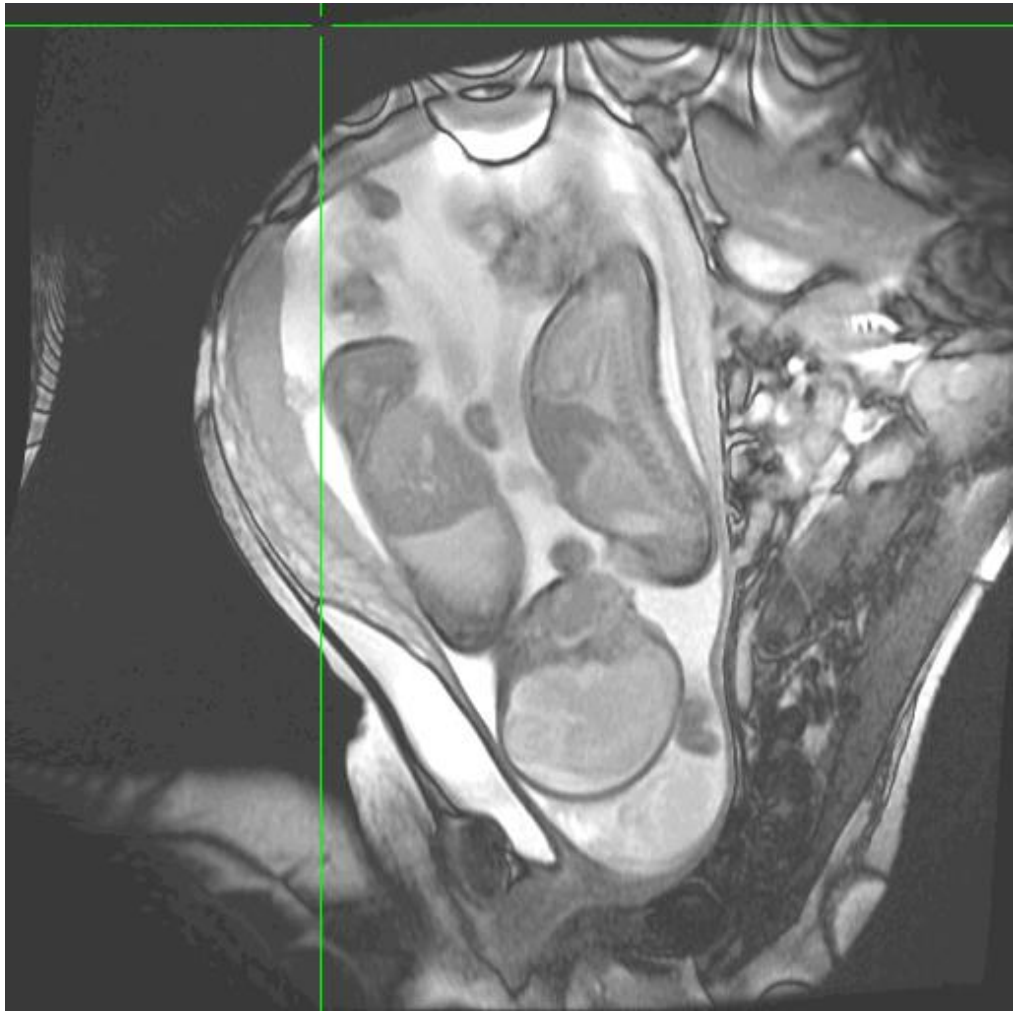
- Navigation to preserve neural circuits.

Computational Radiology Laboratory

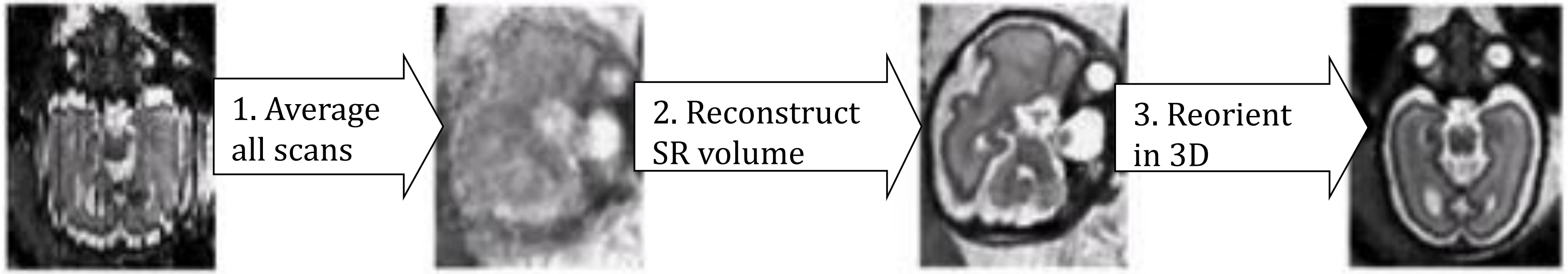




Fetal MRI : motion compensation



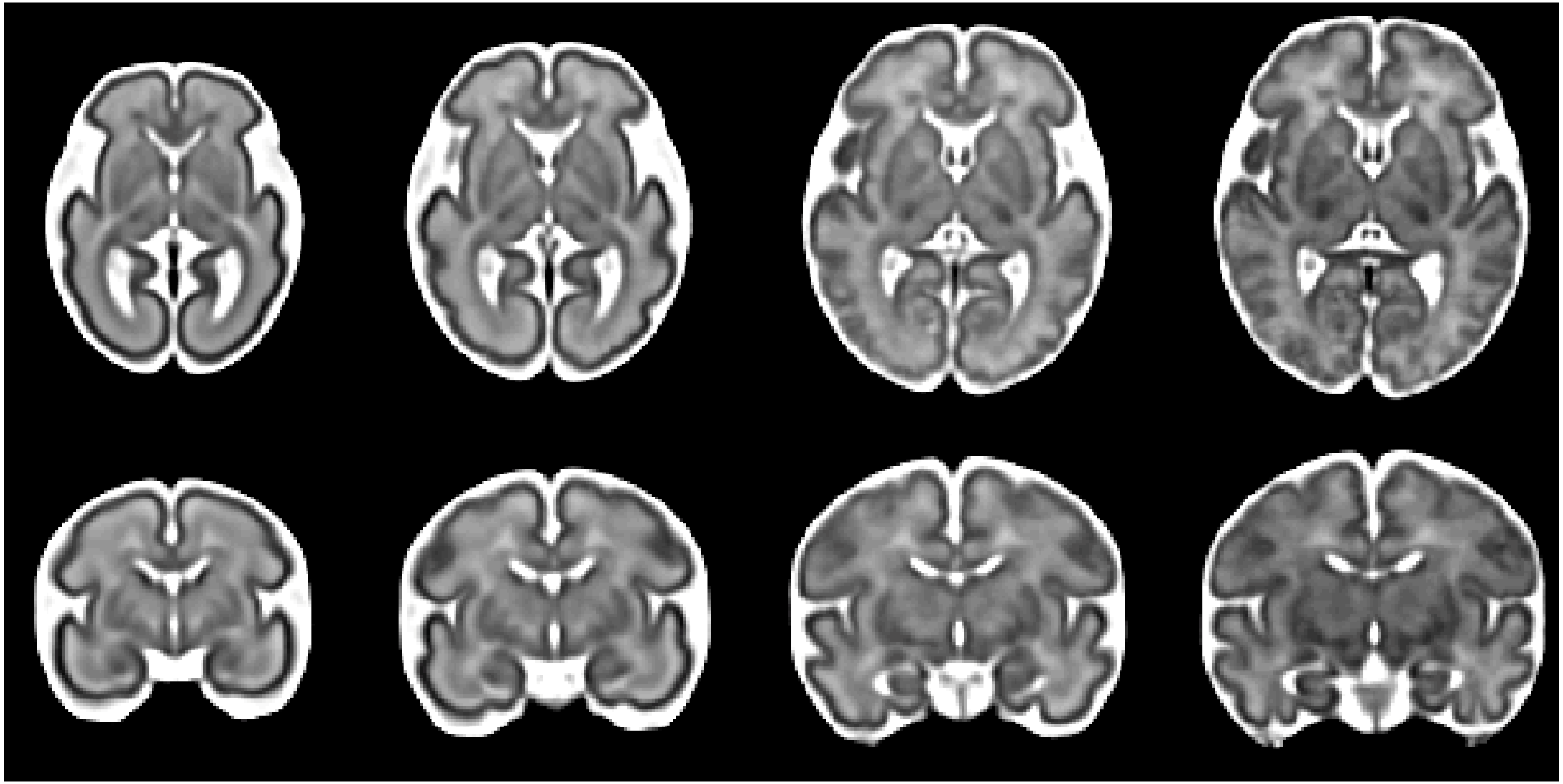
Post-reconstruction processing



- Extract brain (semi-automatic) → intracranial volume

  Simultaneous reconstruction and brain extraction (automatic)
- Correct intensity non-uniformity due to B1 field inhomogeneity
- Register to a common coordinate system (template or atlas)
- A normative spatiotemporal MRI template (22 to 38 weeks GA)
- Atlas labels for fetal brain MRI segmentation
  - Quantitative volumetric and surface-based individual and group analysis

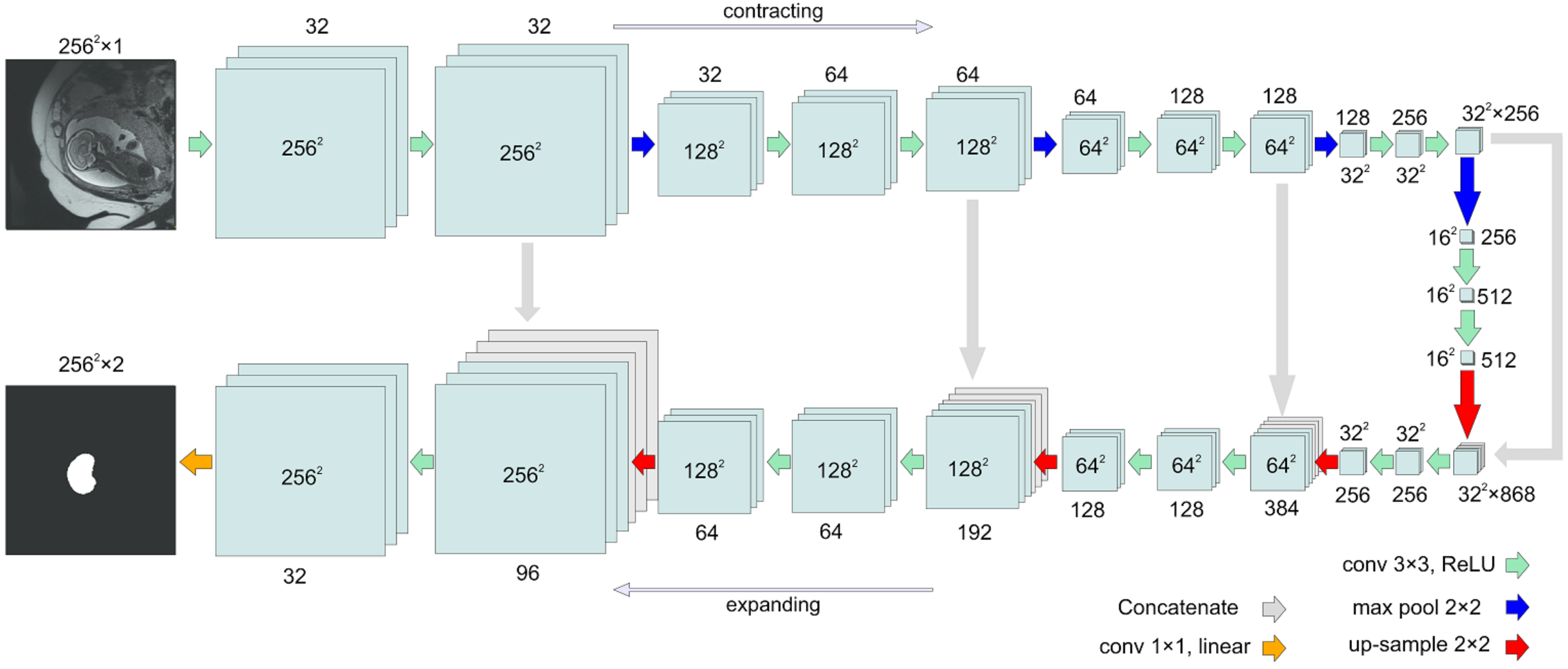
Spatiotemporal fetal brain MRI atlas



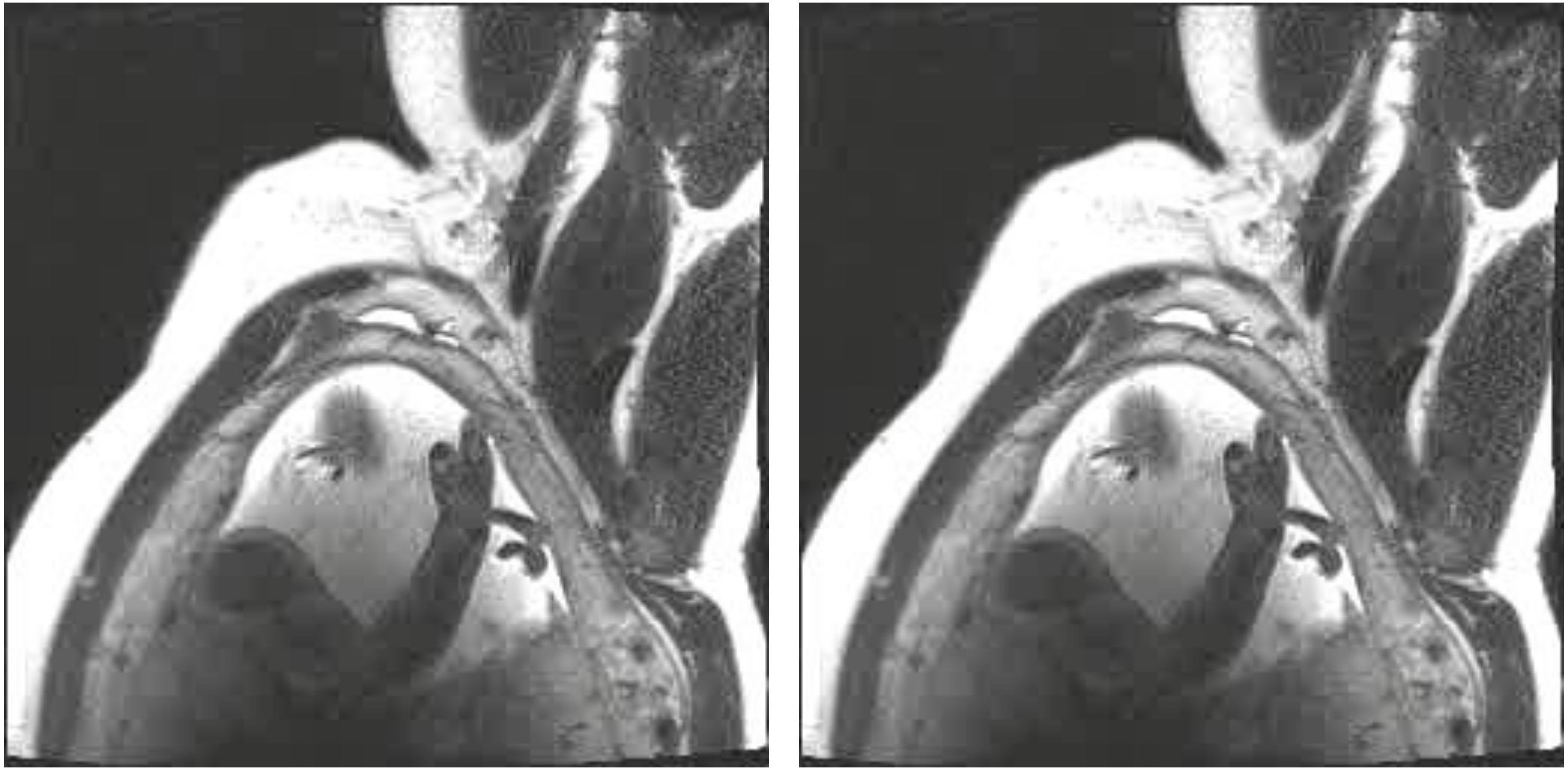
28 weeks | 31 weeks | 34 weeks | 37 weeks

Real-time fetal brain extraction

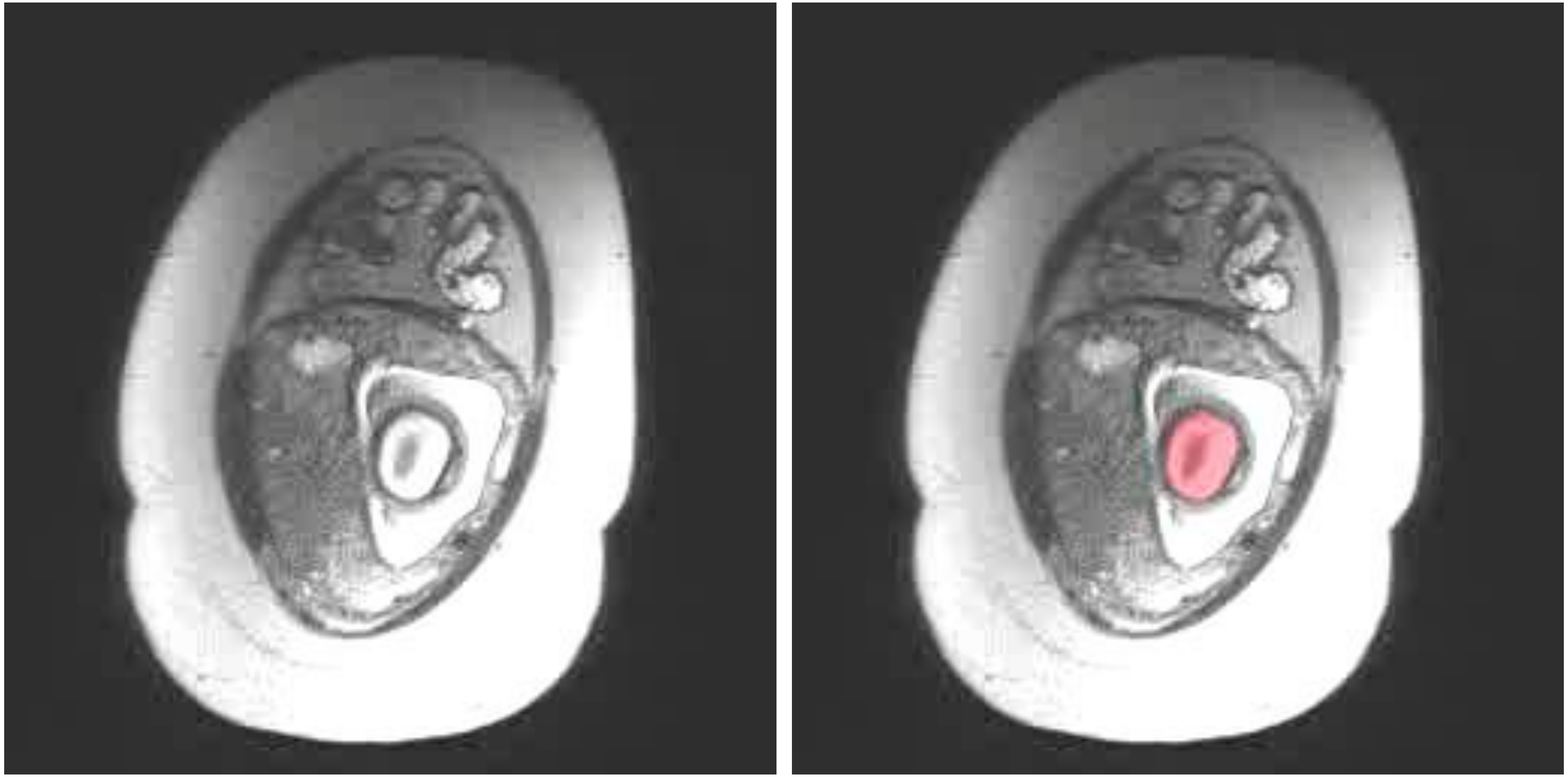
A U-net style deep neural network trained using 250 stacks (~7000 slices) with manual brain masks



Example 1: typical motion

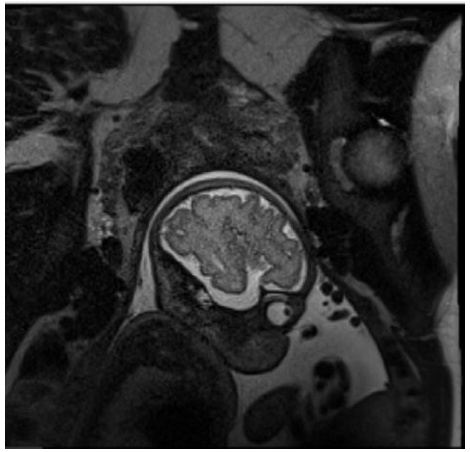


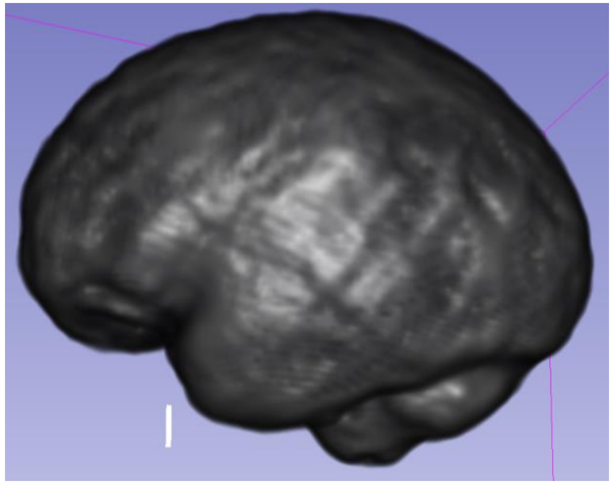
Example 2: substantial fetal motion



Example 3: noisy scan with motion

Real-time 3-D pose estimation

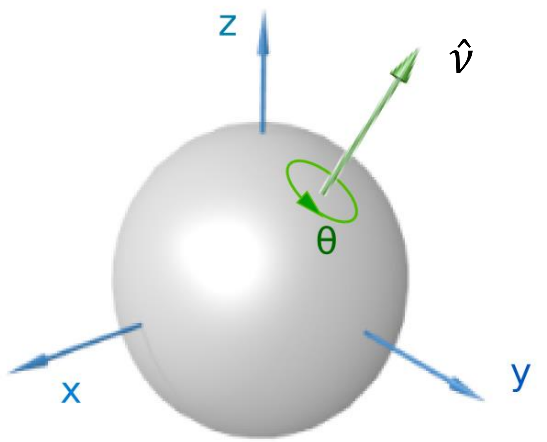




Alignment of each slice / Alignment to Atlas

A little bit of geometry!

Rotation matrix: R_{3x3} , $\begin{cases} Orthogonal \\ detR = 1 \end{cases}$ → 3 DOFs



Axis-angle Representation: Rotation vector v with axis of rotation $\hat{v}$ and an angle around it θ.

Where: $\hat{v} = \frac{v}{\|v\|_2} \quad \theta = \|v\|_2$

Rotation Matrix ↔ Axis-angle

$$\hat{v} = \frac{v}{\|v\|_2} \quad \theta = \|v\|_2$$

$$R = exp(\theta[\hat{v}]_\times)$$

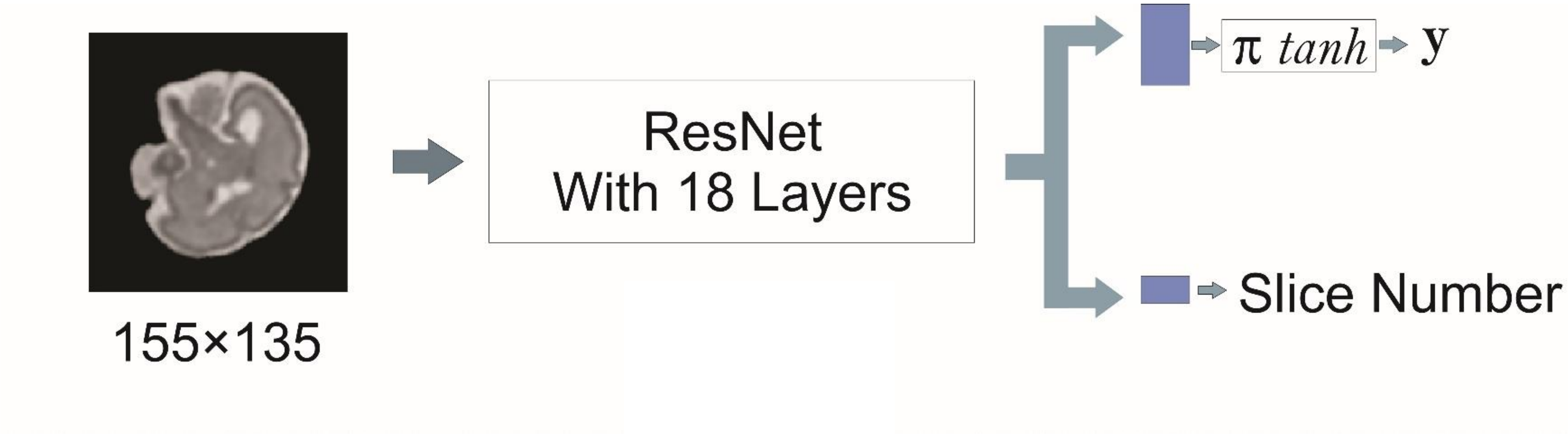
→

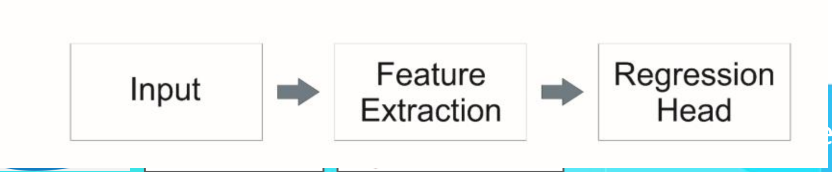
Rodrigues' rotation formula

$$R = I_3 + sin(\theta)[\hat{v}]_\times + (1 - cos\theta)[\hat{v}]_\times^2$$

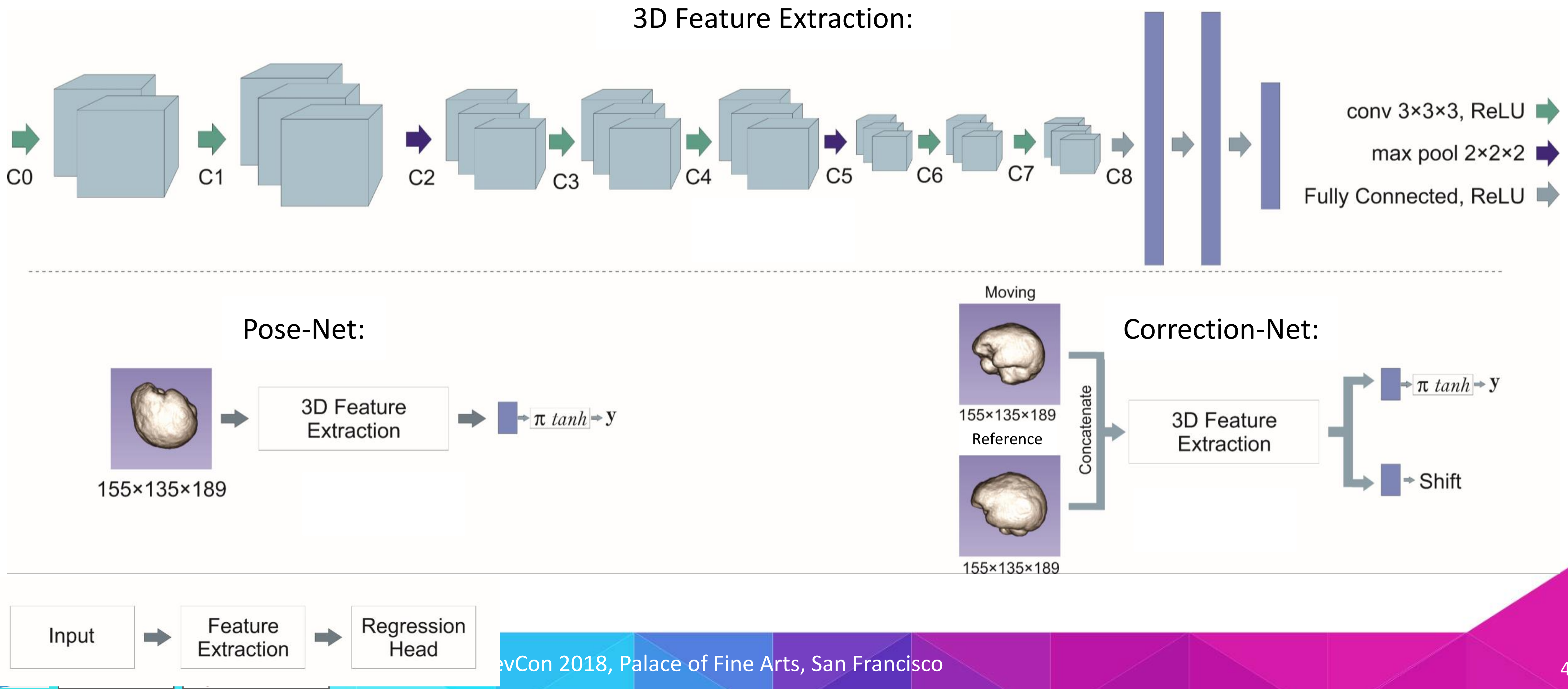
$$\begin{cases} 2sin(\theta)[\hat{v}]_\times = R - R^T \\ tr(R) = 1 + 2cos(\theta) \end{cases}$$

Network Architecture:
(1) Slice-to-Volume Pose Estimation





(2) Volume-to-Volume Pose Estimation

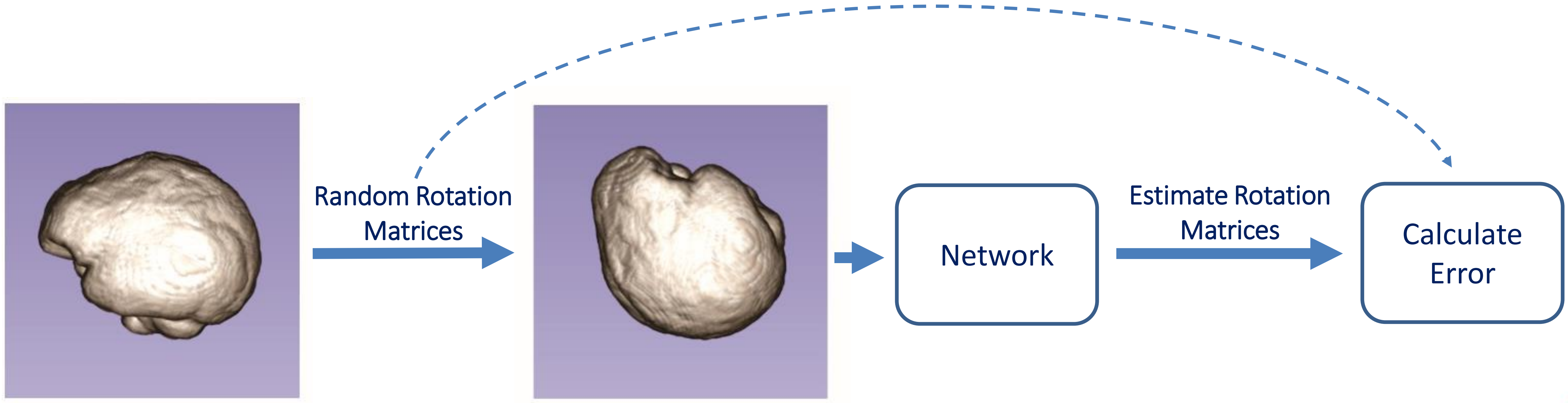


Training

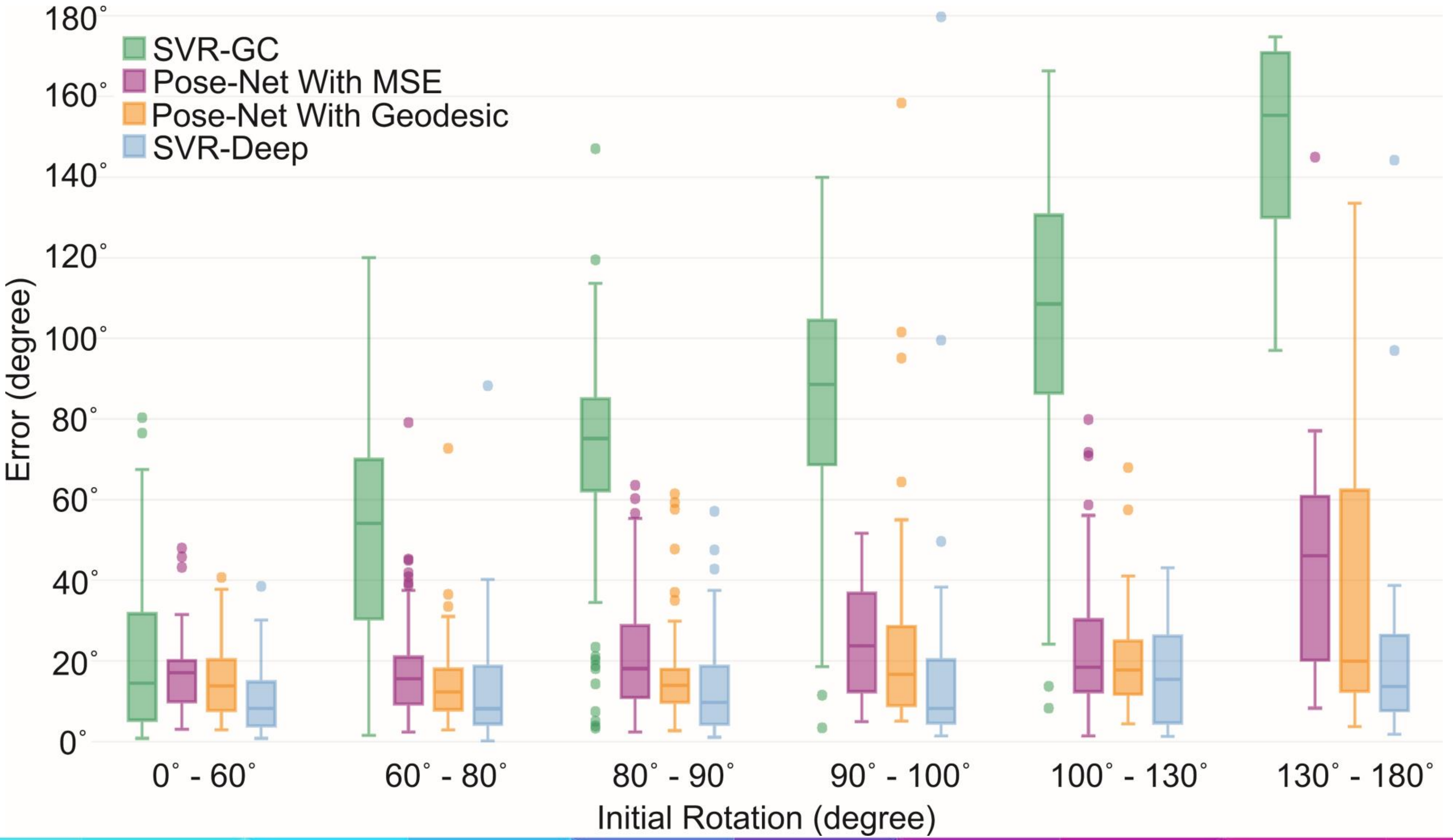
36 Reconstructed image (26-37 weeks)

–5,400,000 slices for Slice To Volume Training

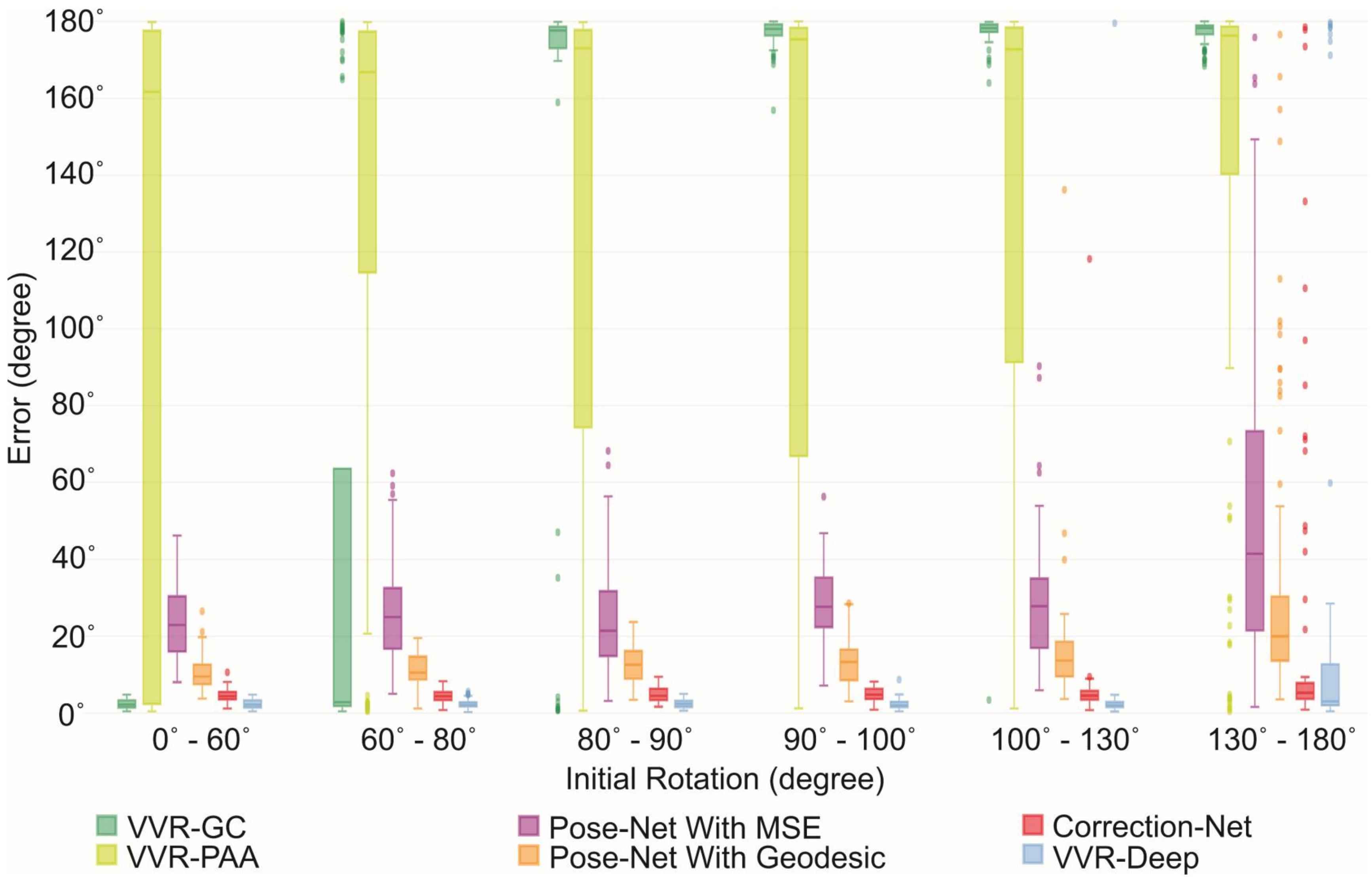
–180,000 volumes for Volume To Volume Training



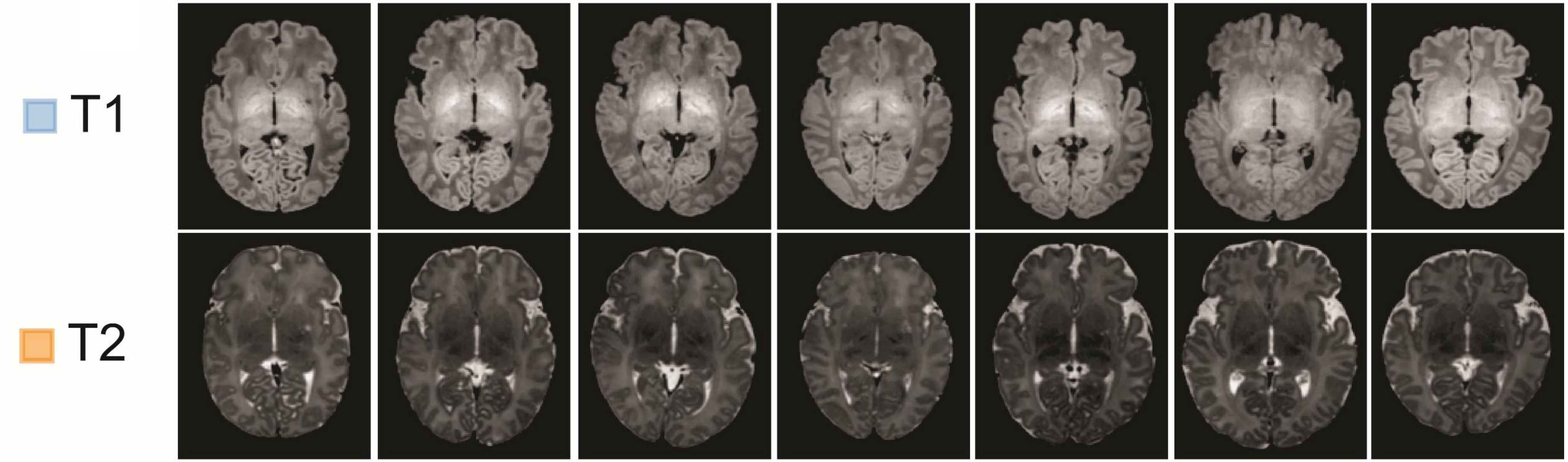
Slice-to-Volume Pose Estimation



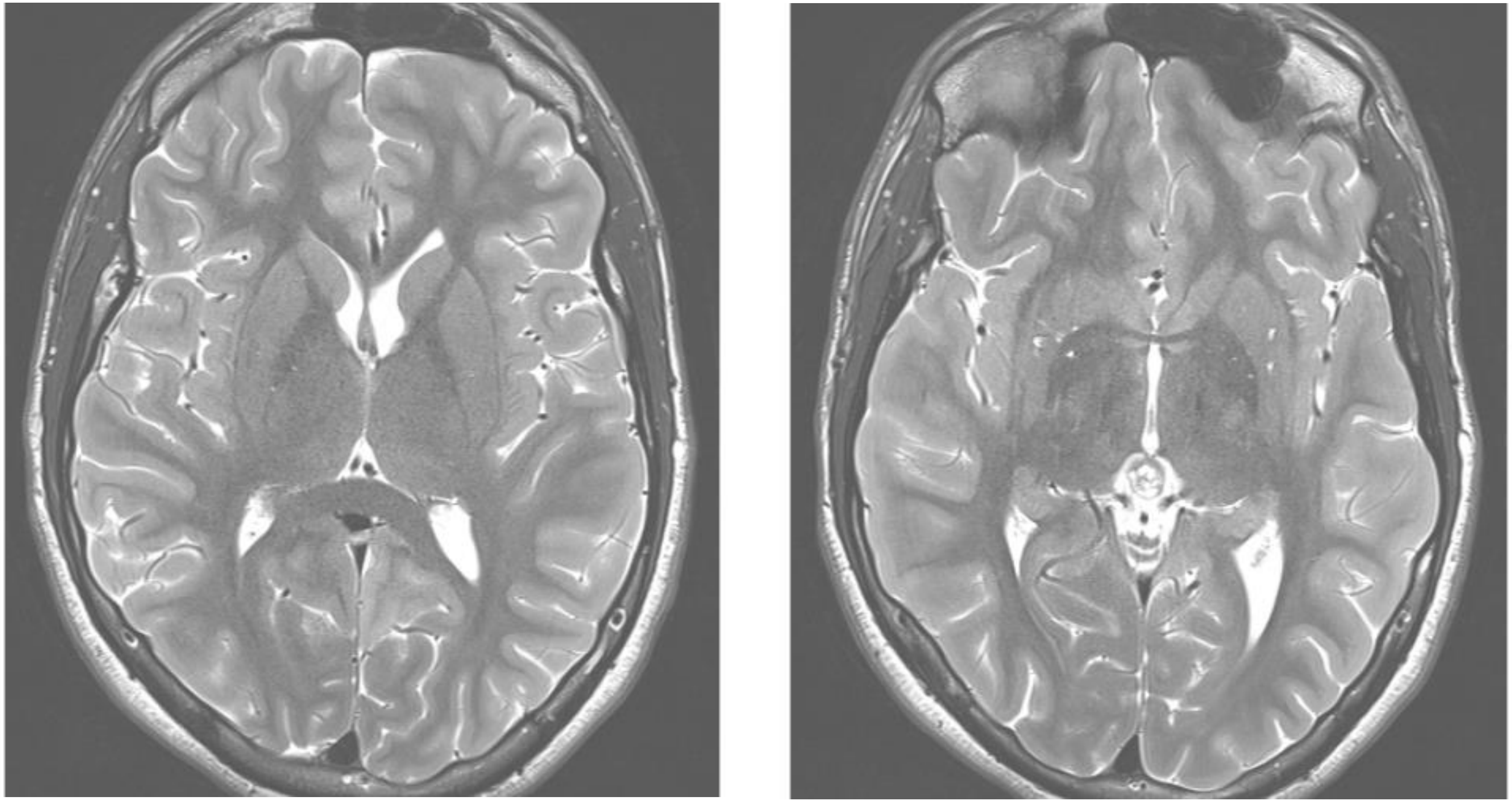
Volume-to-Volume Pose Estimation



Generalization Over Contrasts



Conventional T2 TSE of FCD from 3T MRI

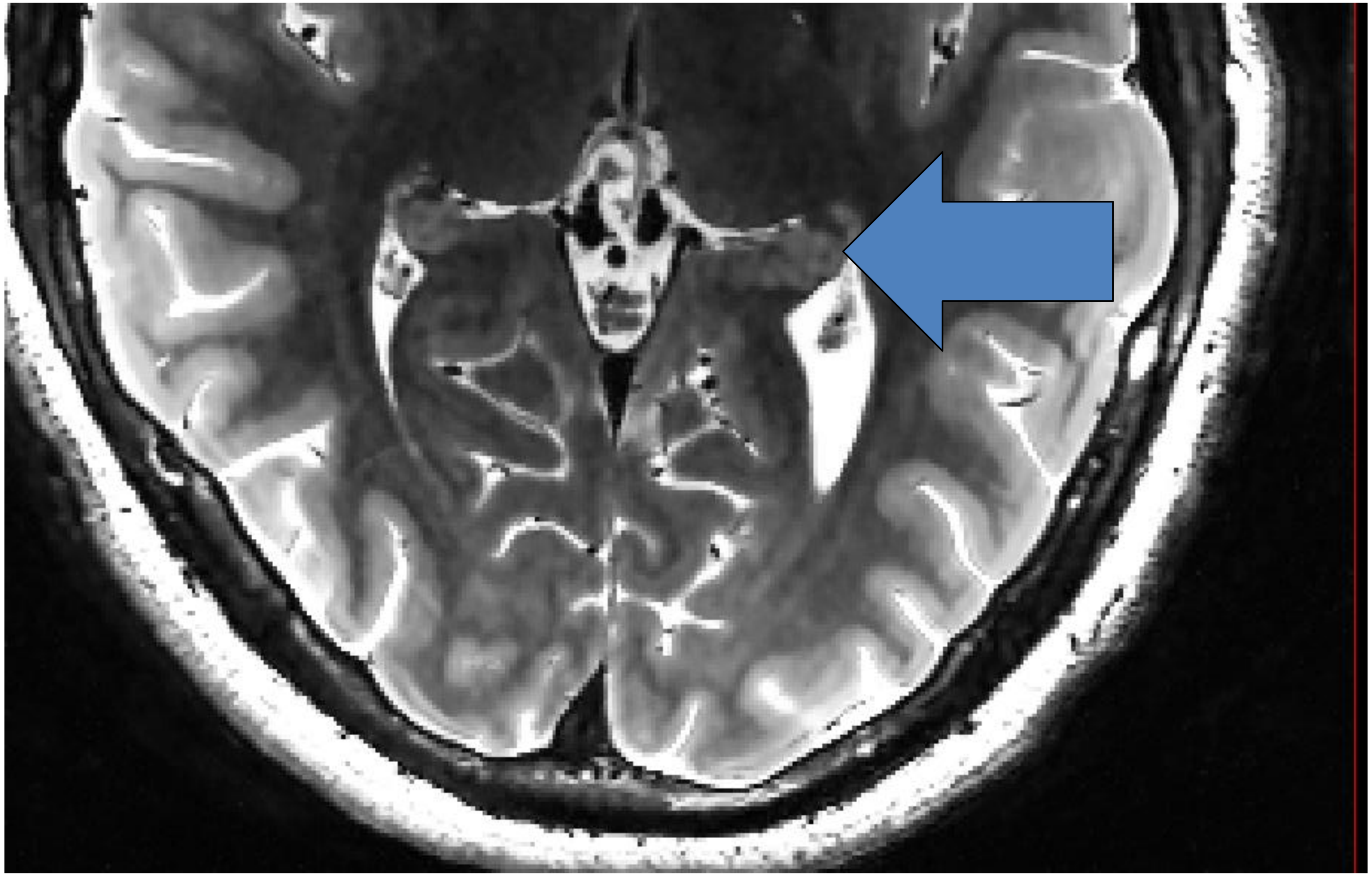


Voxel size 0.5x0.5x2.5 cubic mm

MR Image Reconstruction

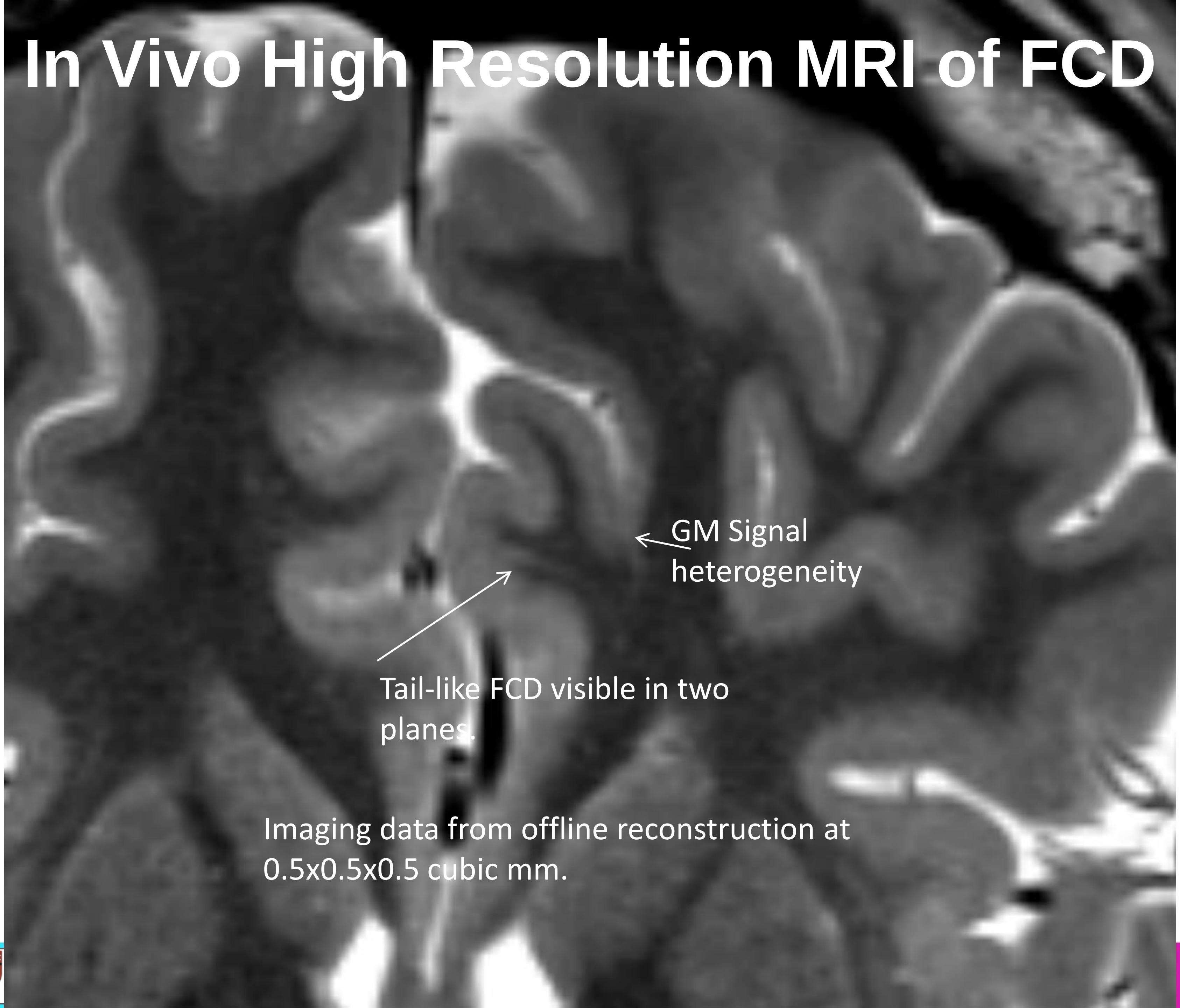
- Optimal reconstruction requires precise knowledge of the coil spatial sensitivity and the noise covariance structure of the array of coils.
- Approximations used in practice limit the sensitivity, as they are appropriate only in the high SNR regime.
- We developed improved coil to coil covariance structure estimation, and coil sensitivity profile estimation.
- We account for time varying properties of the scanner that occur during long acquisitions.
- About 1TB of raw data on a 64 channel head coil, long image reconstruction time.

In Vivo High Resolution MRI of FCD



Improved detection and determination of the extent of the FCD
Voxel size 0.5x0.5x0.5 cubic mm

In Vivo High Resolution MRI of FCD



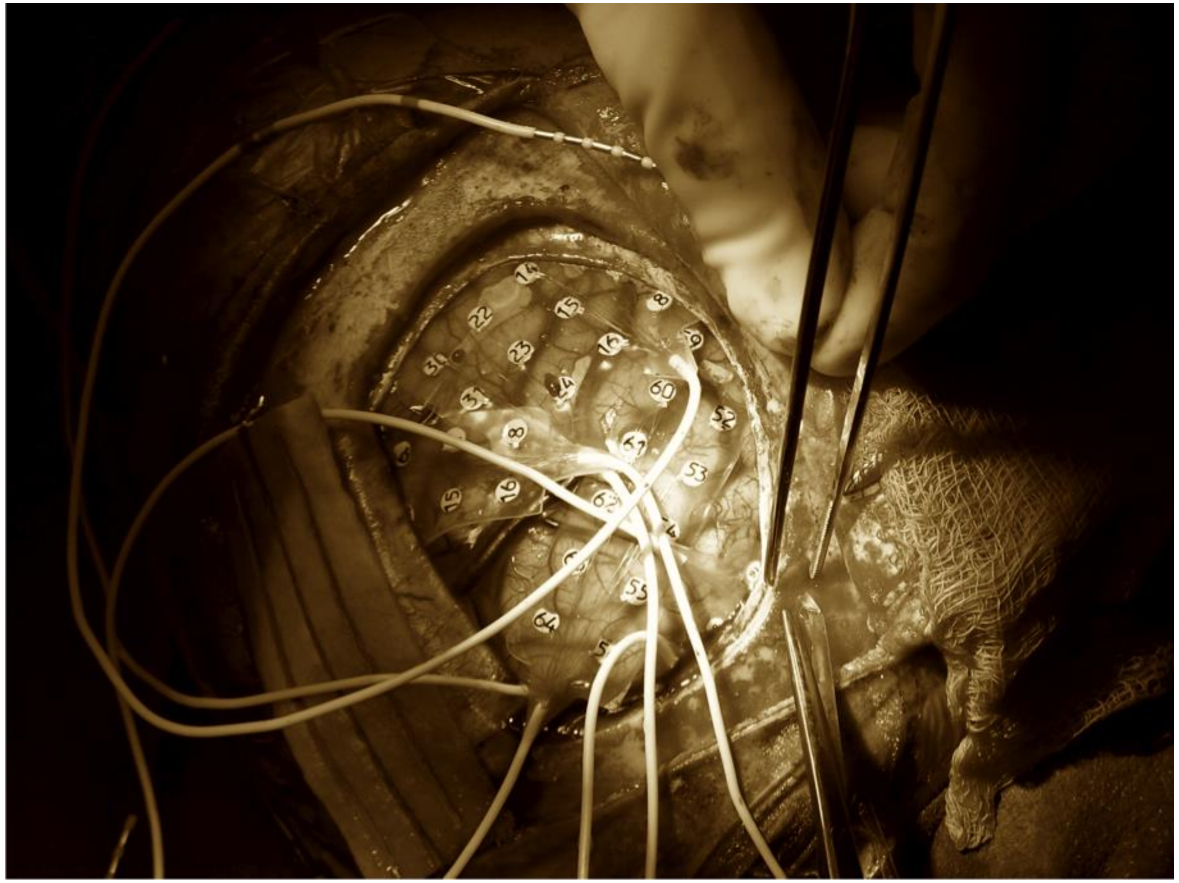
EEG/MEG Source Imaging

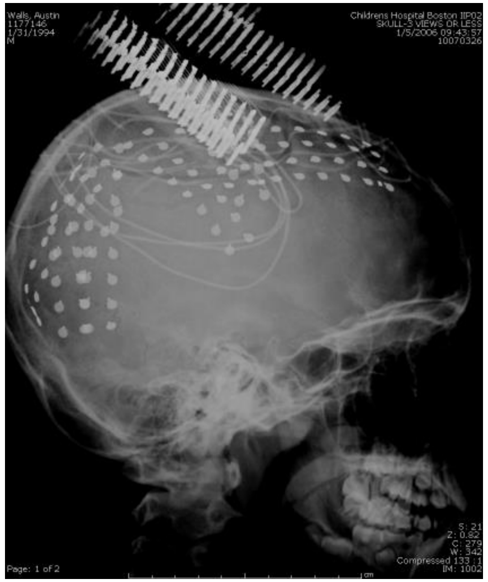
- Noninvasive measurements

128 channel EEG

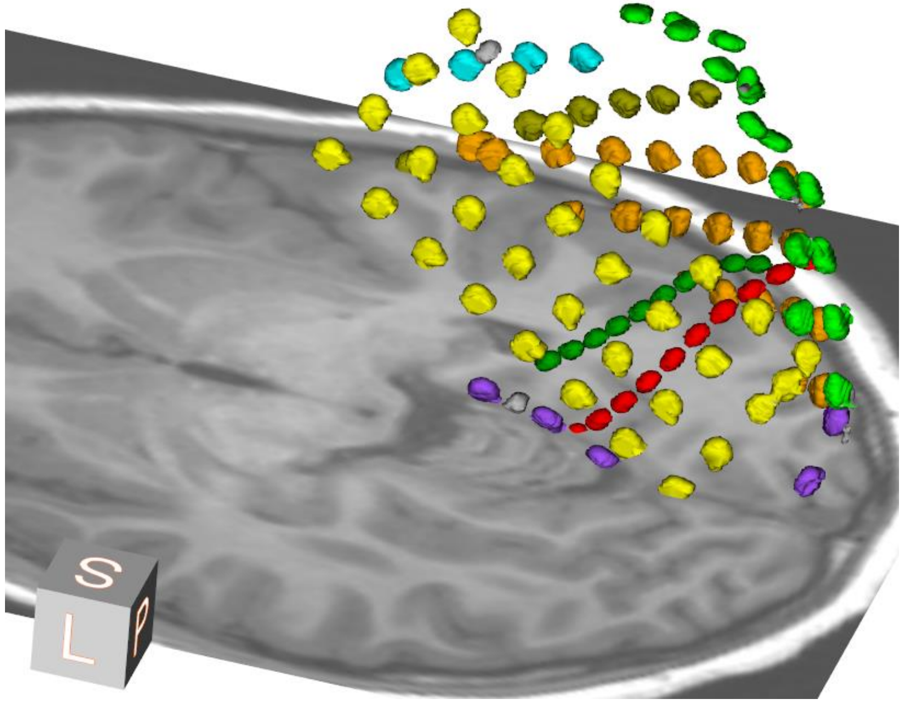
MEG

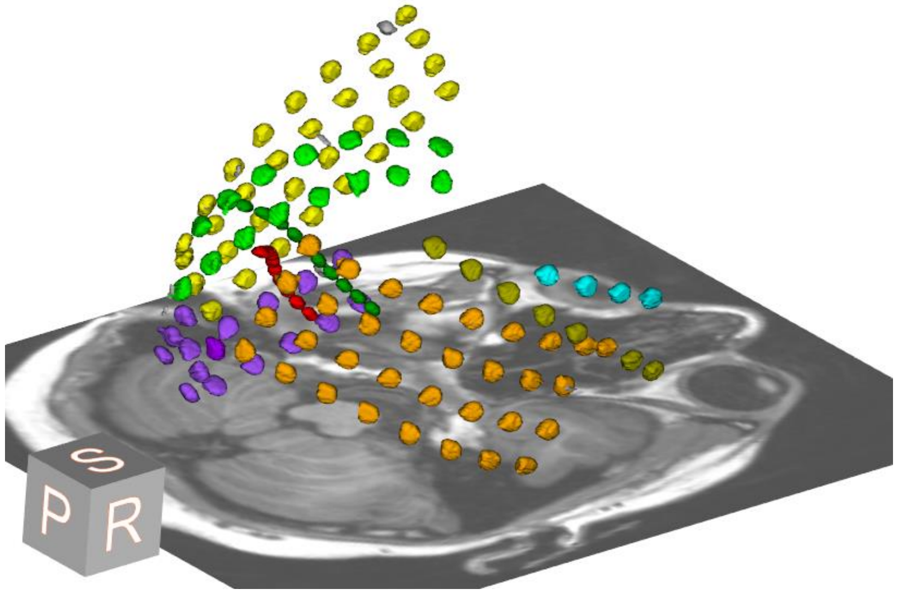
Invasive Source Localization



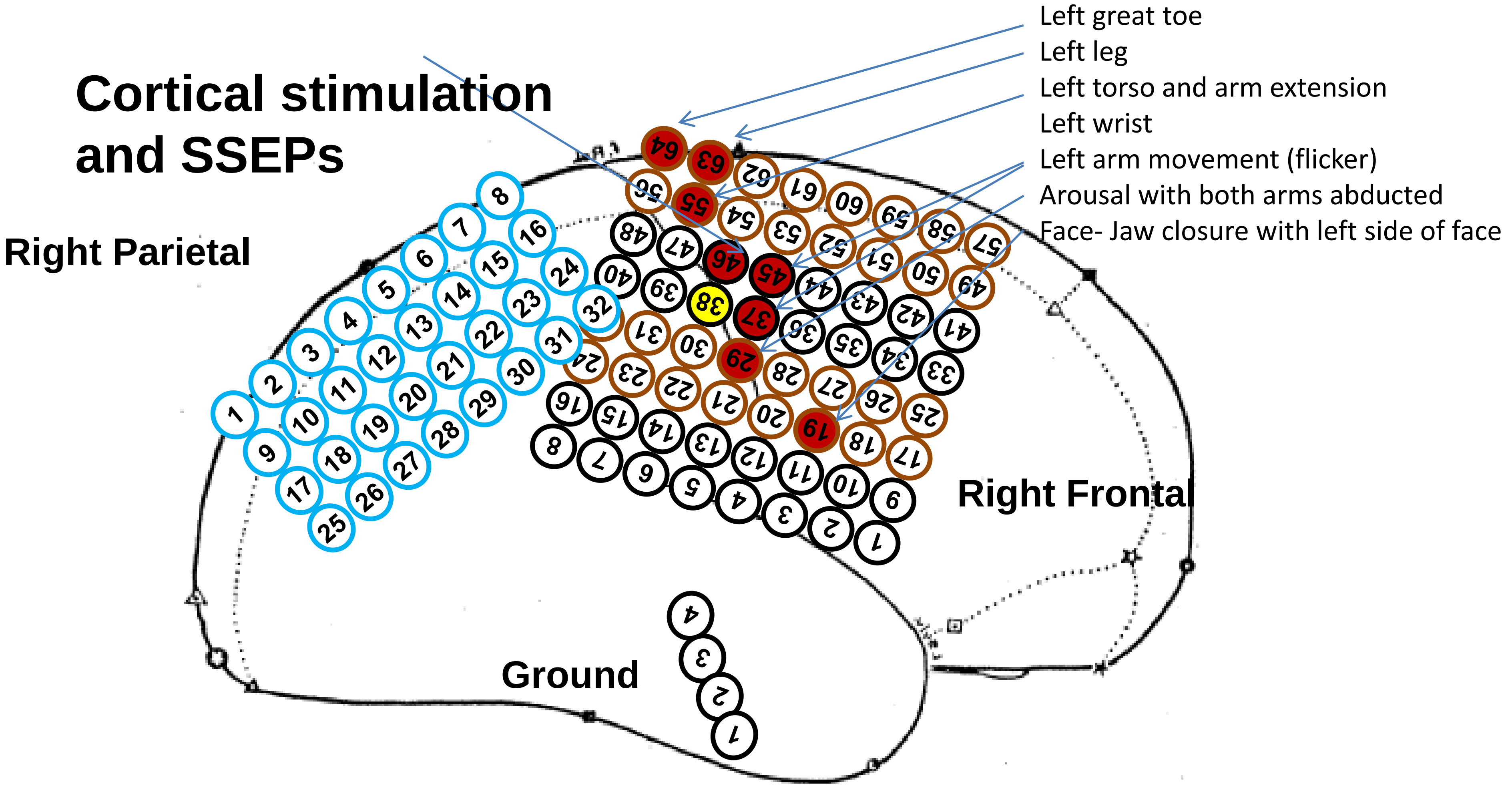


3D visualization of electrodes

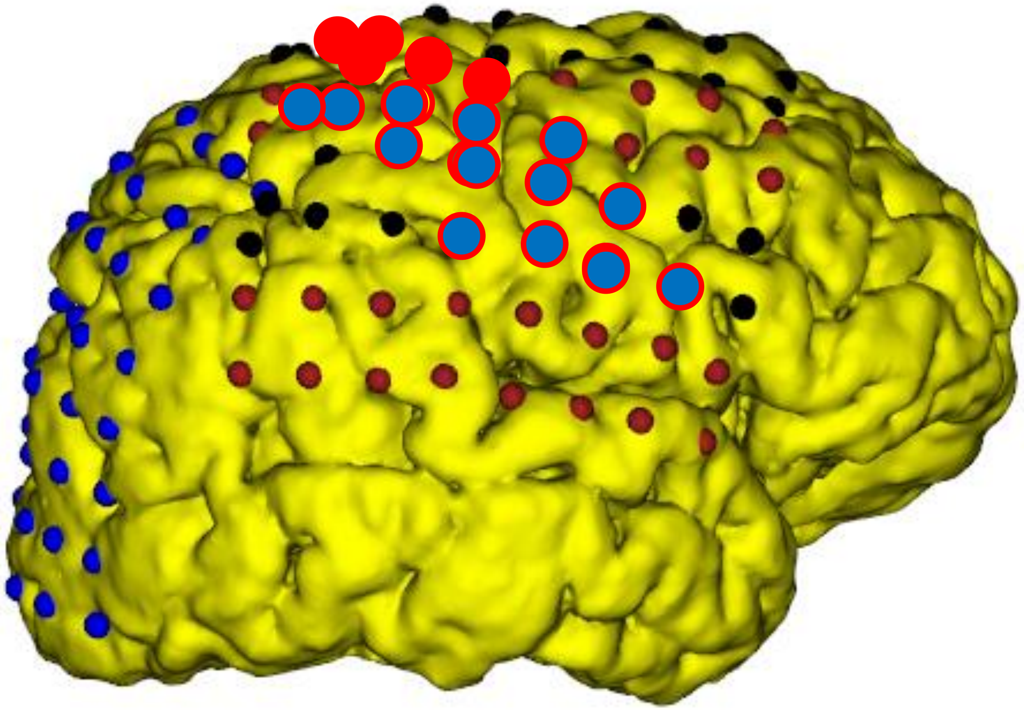




Cortical stimulation and SSEPs

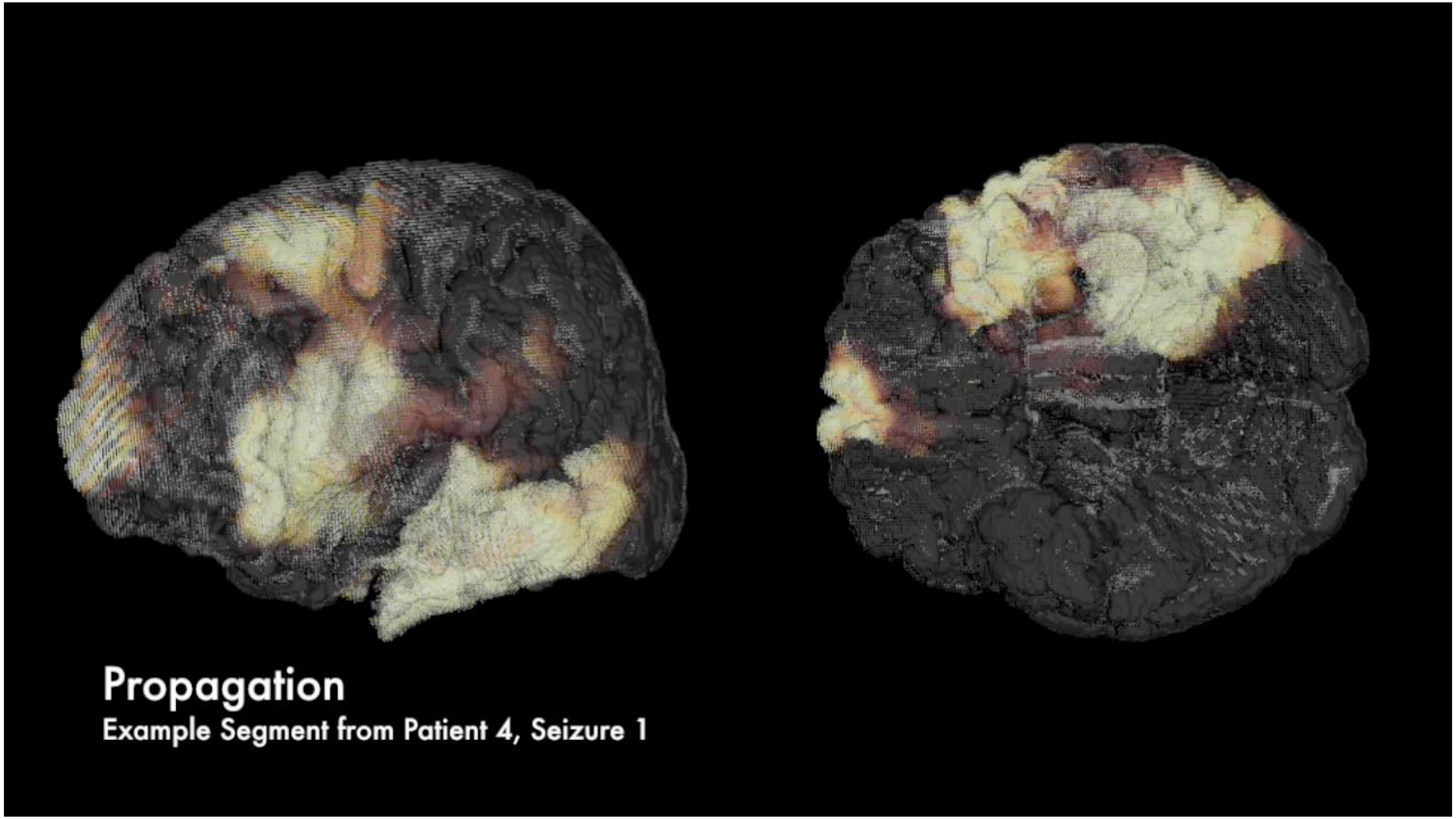


Right

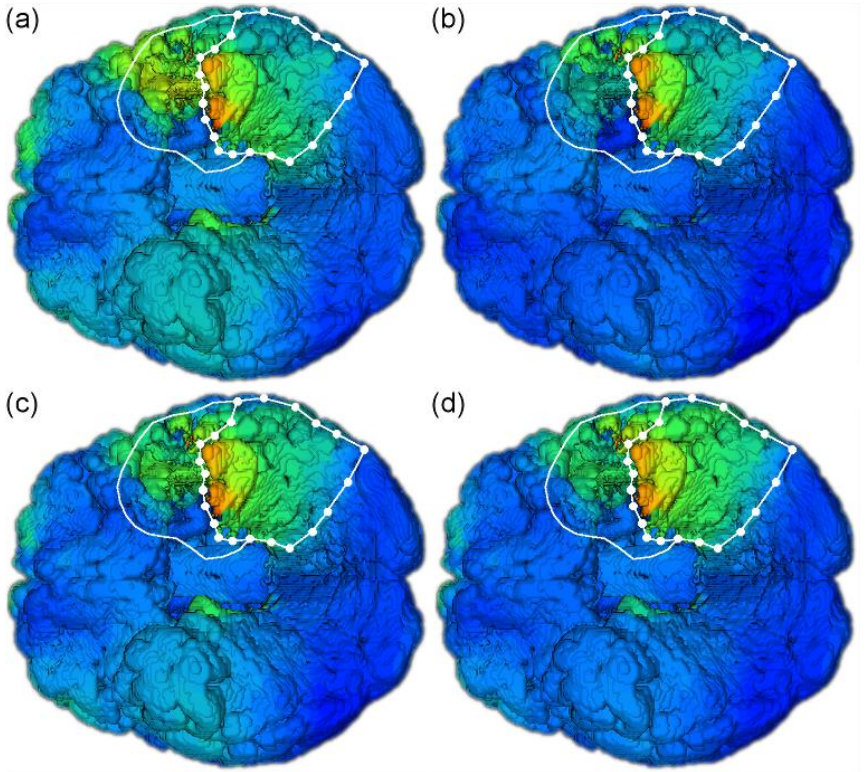


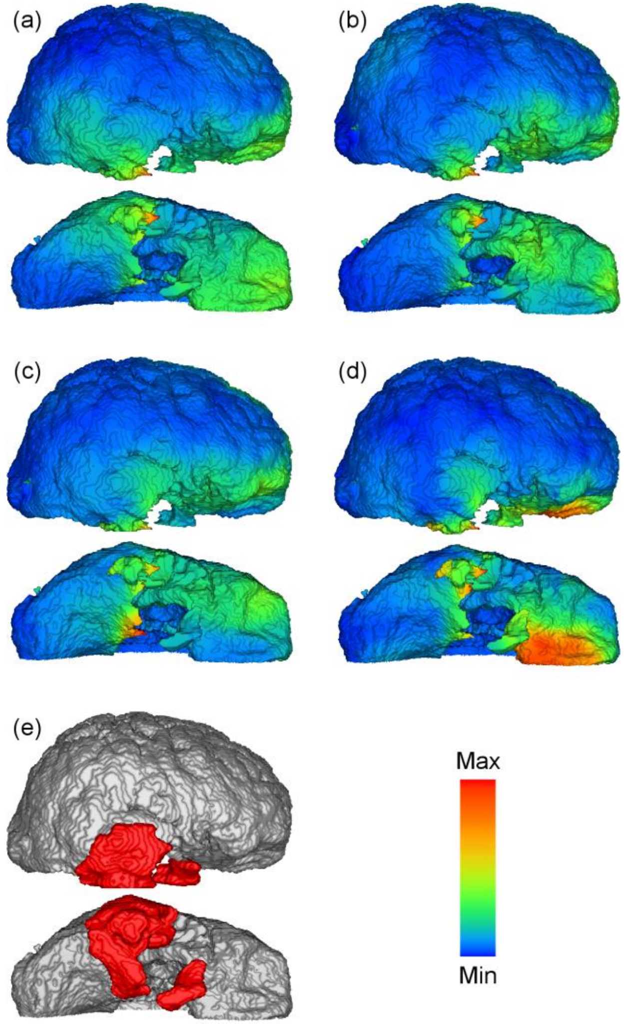
SSEP
Motor
RF 29

Common
seizure spread


Propagation
Example Segment from Patient 4, Seizure 1

Cumulative Activity Maps





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Computational Radiology Laboratory

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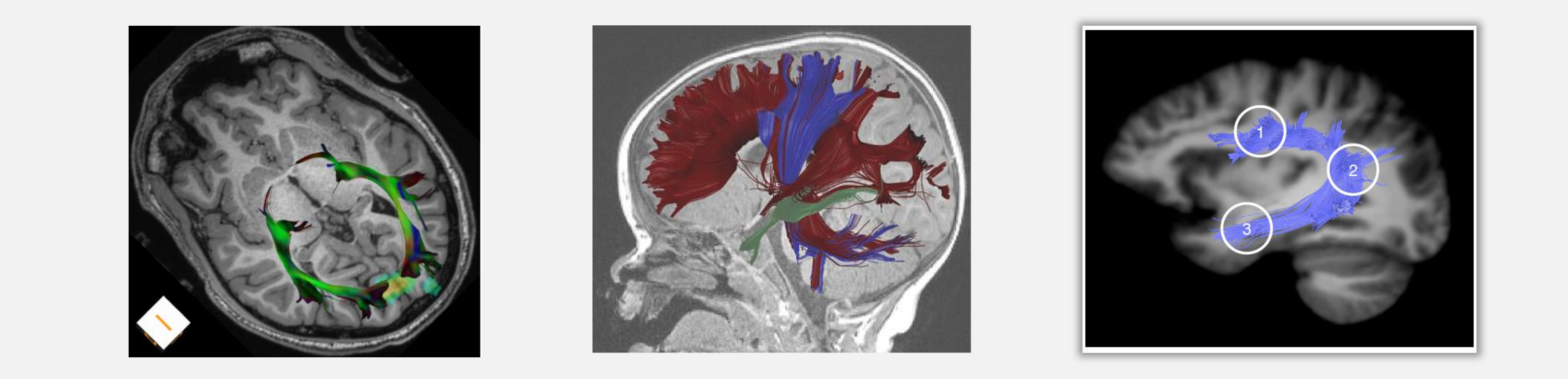

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