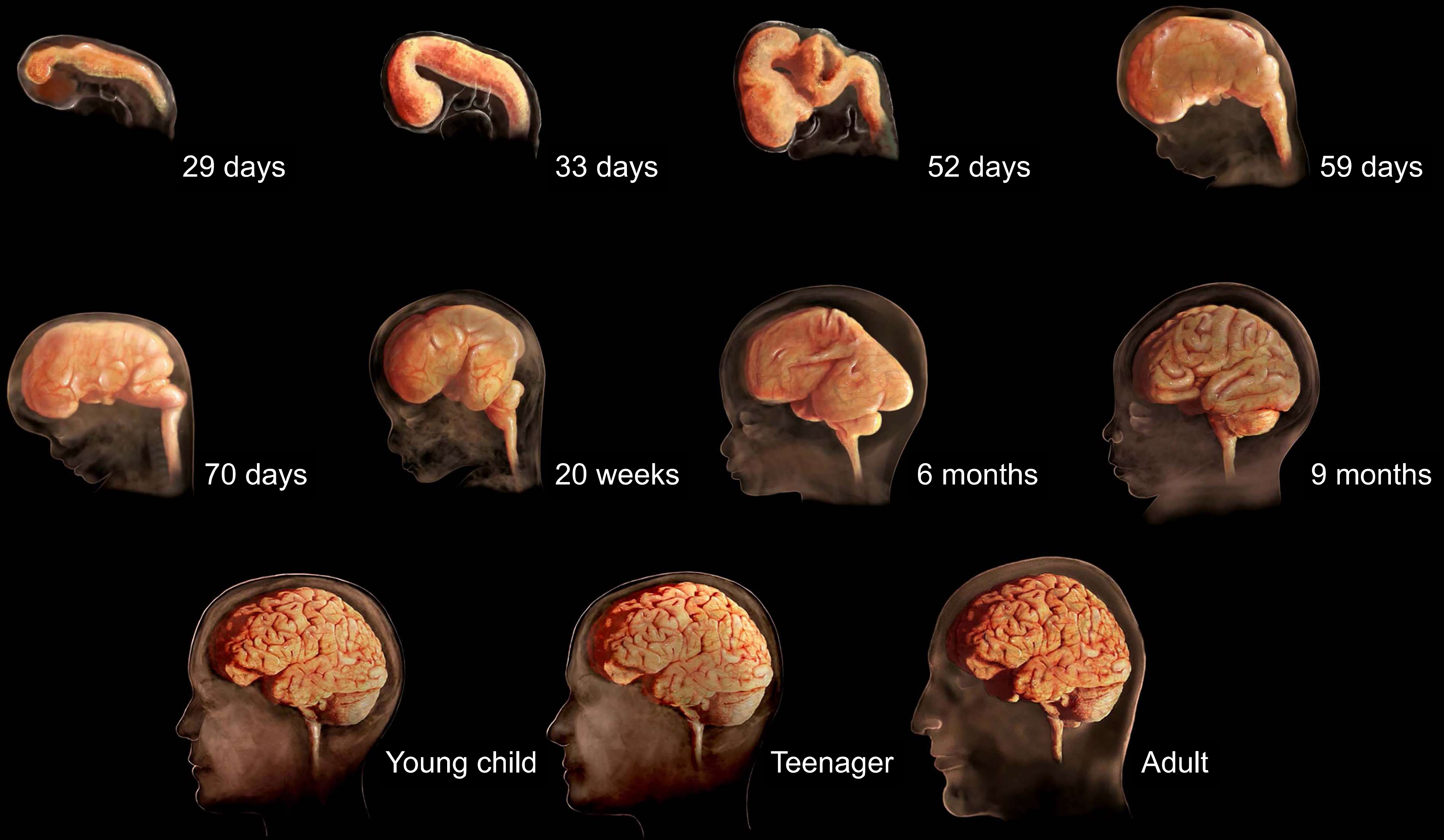
THE RAPID CHANGE OF DEVELOPING BRAINS



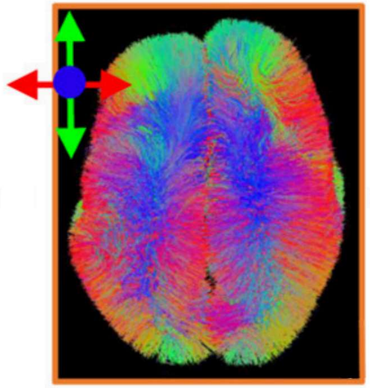
Konkel, Environmental Health Perspectives, 2018

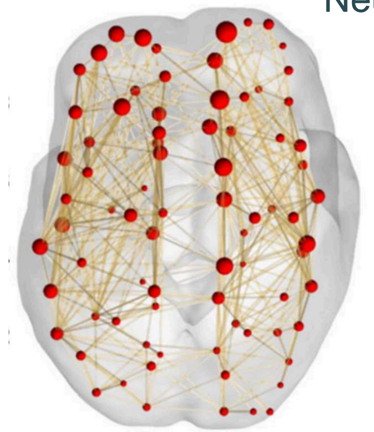
DIFFUSION MRI IN DEVELOPING BRAINS

- Research motivations
  - Assessment of brain maturation and white matter development
  - Macroscale connectivity
  - Comparative analyses (pathologies, species)
  - Longitudinal studies from *in utero*

- Clinical motivations[1]
  - Cytoxic (intra-cellular) edema
  - Vasogenic (extra-cellular) edema

Figure from Afif et al., Brain Structure and Function 2007





Adapted from Song et al., Frontiers in Neuroscience 2017

[1] Garel. MRI of the Fetal Brain. Springer (2004)

DIFFUSION MRI IN DEVELOPING BRAINS

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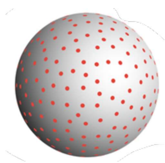
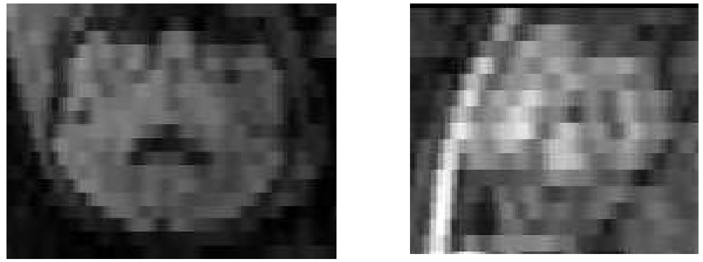
- MAIN CHALLENGES
  - Low signal-to-noise ratio/low (through-plane) spatial resolution

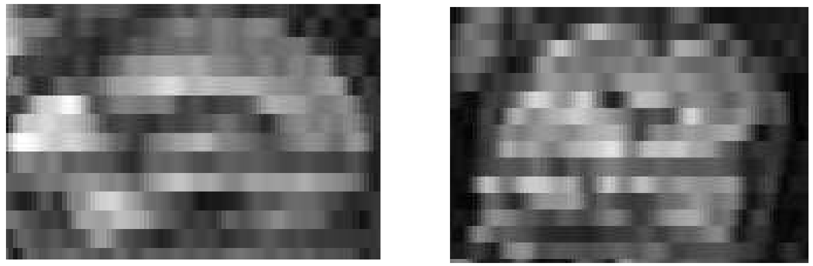
  - Motion
  - Diffusion MRI distortion artefacts
  - Protocol restrictions (small and unique b-values, limited number of gradient directions)



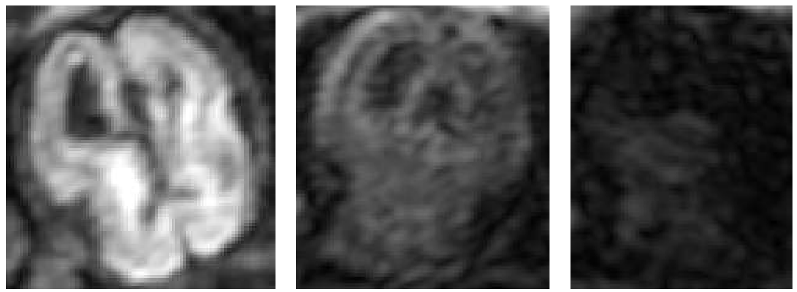
  - Rapidly developing anatomy
  - Gradient directions mismatch



Low through-plane resolution



Intra-volume motion



Inter-volumes motion and signal drop

Robust estimation of the microstructure of the early developing brain using deep learning

Hamza Kebiri[1,2,3], Ali Gholipour[3], Rizhong Lin[2,4], Lana Vasung[5], and Davood Karimi[3,⋆], Meritxell Bach Cuadra[1,2,⋆]

[1] CIBM Center for Biomedical Imaging, Switzerland
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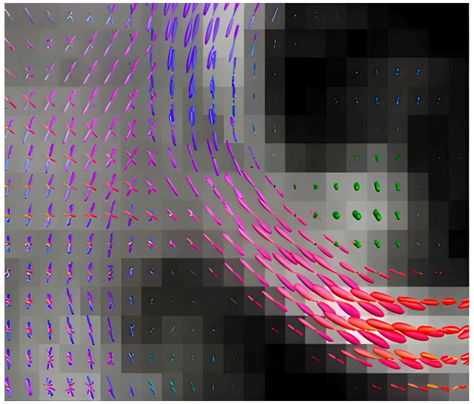
[3] Computational Radiology Laboratory, Department of Radiology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA
[4] Signal Processing Laboratory 5 (LTS5), École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
[5] Department of Pediatrics, Boston Children's Hospital, and Harvard Medical School, Boston, Massachusetts, USA

MICCAI 2023; ISMRM *2023; Medical Image Analysis (under revision) 2023*

https://link.springer.com/chapter/10.1007/978-3-031-43990-2_28

CONTEXT

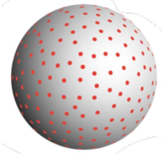


Adapted from Shi and Toga, Molecular Psychiatry, 2017

- Microstructure best estimated with fiber orientation distribution function (FODs)

- Problem
  - High number of measurements and high/multiple b-values requirement for accurate estimation with widely used state-of-the-art methods[1,2]

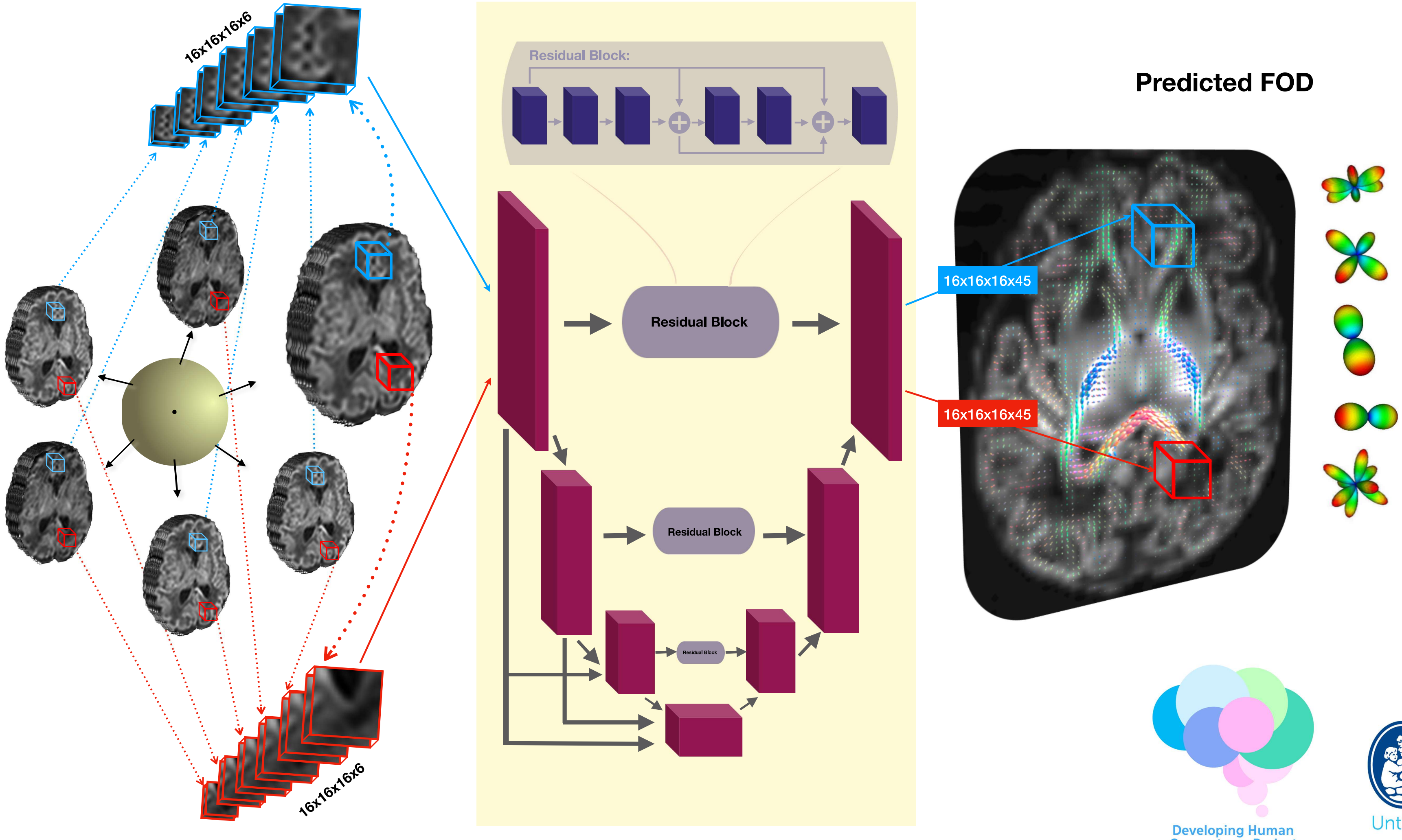
    BUT: Unrealistic for developing brains!



- Proposed solution
  - Use deep neural networks and available research dedicated datasets to learn a mapping between few measurements and target diffusion metrics (FOD, tensor, scalar map, etc.)

[1] Tournier et al., Neuroimage, 2007; [2] Jeurissen et al., Neuroimage, 2014

PROPOSED MODEL



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Developing Human Connectome Project

Boston Children's Hospital
Until every child is well

NETWORKS & DATA

- Input: 6 or 12 b0-normalized diffusion measurements (in spherical harmonics basis)
- Output: 45 SH coefficients of FOD estimated with multi-shell multi-tissue constrained spherical deconvolution (MSMT-CSD)[1] using all 300 multi-shell dHCP[2,3] measurements
- Two networks:

(1) ***Newborn network*** trained on dHCP newborn subjects and evaluated **quantitatively** on dHCP newborn subjects and ***qualitatively*** on clinical newborns subjects from Boston Children's Hospital (BCH)

(2) ***Pre-term network*** trained on dHCP pre-term subjects and evaluated **qualitatively** on clinical fetal subjects from BCH

[1] Jeurissen et al., Neuroimage, 2014; [2] Hutter et al., MRM, 2018; [3] Tournier et al., NMR in Biomedicine, 2020

NETWORKS & DATA

- *Newborns network* (trained and tested on dHCP newborns[2,3] and clinical newborns)
  - Training/validation: 145 subjects of post-menstrual age (PMA) [26-45] weeks
  - Testing: 320 dHCP subjects; 15 BCH subjects (PMA [38-48] weeks)
  - 6 input uniform[1] measurements
  - b = 1000 s/mm^2

- *Pre-term network* (trained on pre-term newborns[2,3] and tested on fetuses)
  - Training/validation: 77 pre-terms of PMA [26, 38] weeks
  - Testing: 11 fetal subject ([24, 38] gestational weeks)
  - 12 input measurements
  - Pre-terms at b=400 s/mm^2 and fetuses at b=500 s/mm^2

[1] Skare et al., JMR, 2000

MODEL EVALUATION

- Baseline models
  - Constrained Spherical Deconvolution (CSD)[1] with 148 measurements
  - Constant Solid Angle[2] with 300 measurements
  - Sparse Fascicle Model (SFM)[3] with 300 measurements
  - Multi-layer perceptron (MLP)[4]
  - CTtrack (CNN + Transformers)[5]
- Ground truth agreement (ΔGS)
  - Spliting the ground truth into two disjoint gold standard (GS) subsets of 150 measurements each

[1] Tournier et al., Neuroimage, 2007; [2] Aganj et al., MRM, 2010; [3] Rokem et al., PloS one, 2015 ; [4] Karimi et al., Neuroimage, 2021; [5] Hosseini et al., Neuro. Informatics, 2022

MODEL EVALUATION

- dHCP newborns evaluation
  - Agreement rate (AR) in number of peaks
  - Angular error
  - Apparent Fiber Density[1]

	1 peaks	2 peaks	3 peaks
1 peaks	a_{11}	a_{12}	a_{13}
2 peaks	a_{21}	a_{22}	a_{23}
3 peaks	a_{31}	a_{32}	a_{33}

$$AR_{1\text{-peaks}} = a_{11} / (a_{11} + a_{12} + a_{13} + a_{21} + a_{31})$$

$$AR_{2\text{-peaks}} = a_{22} / (a_{22} + a_{21} + a_{23} + a_{12} + a_{32})$$

$$AR_{3\text{-peaks}} = a_{33} / (a_{33} + a_{32} + a_{31} + a_{23} + a_{13})$$

- Clinical newborns evaluation
  - Visual assessment by an expert neuroanatomist
- Fetal evaluation
  - Visual assessment by an expert neuroanatomist
  - Histological comparison with post-mortem brains

Boston Children's Hospital
Until every child is well

Croatian Institute For Brain Research

[1] Rafflet et al., Neuroimage, 2012

QUALITATIVE RESULTS: DHCP NEWBORNS

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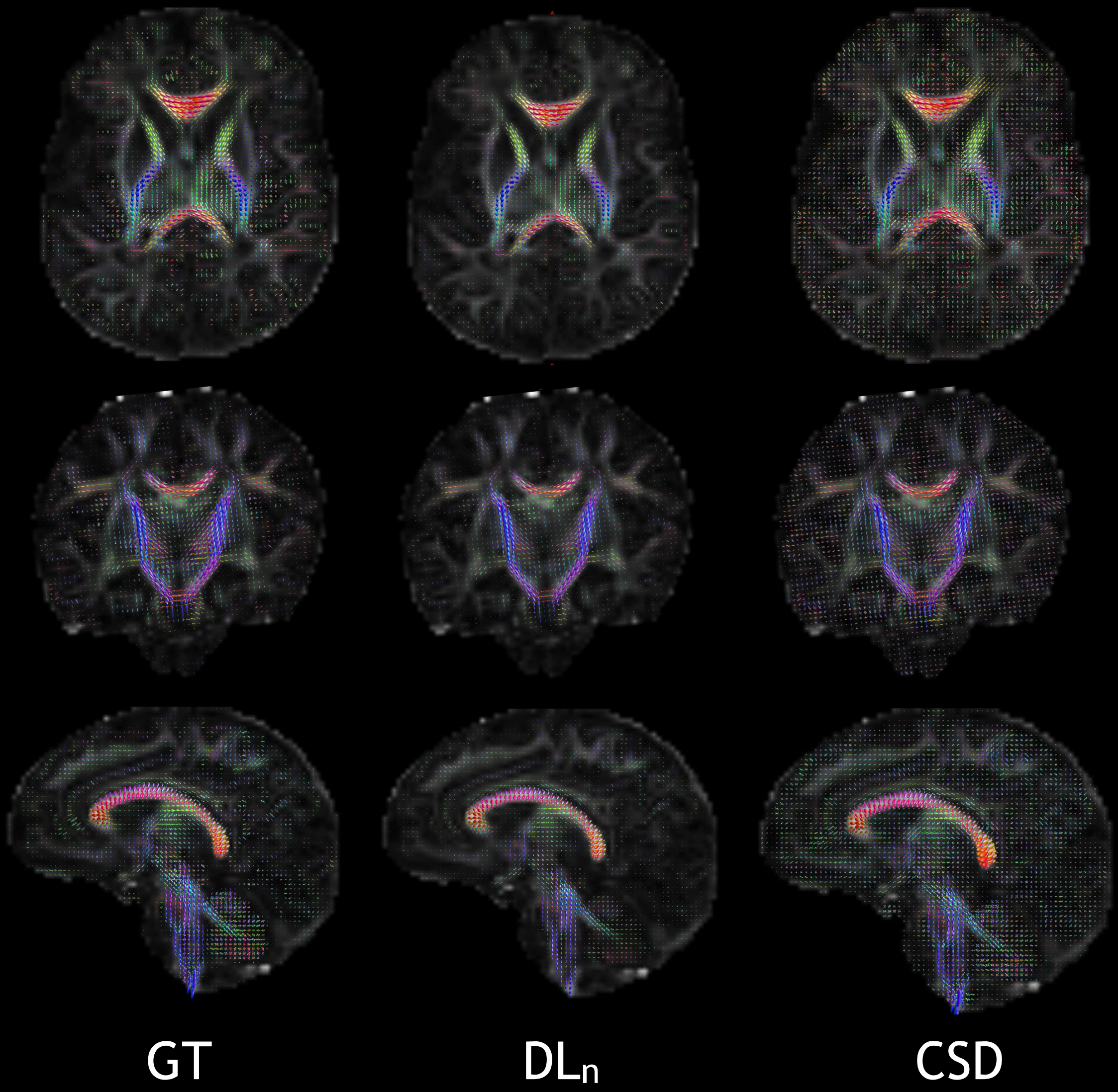
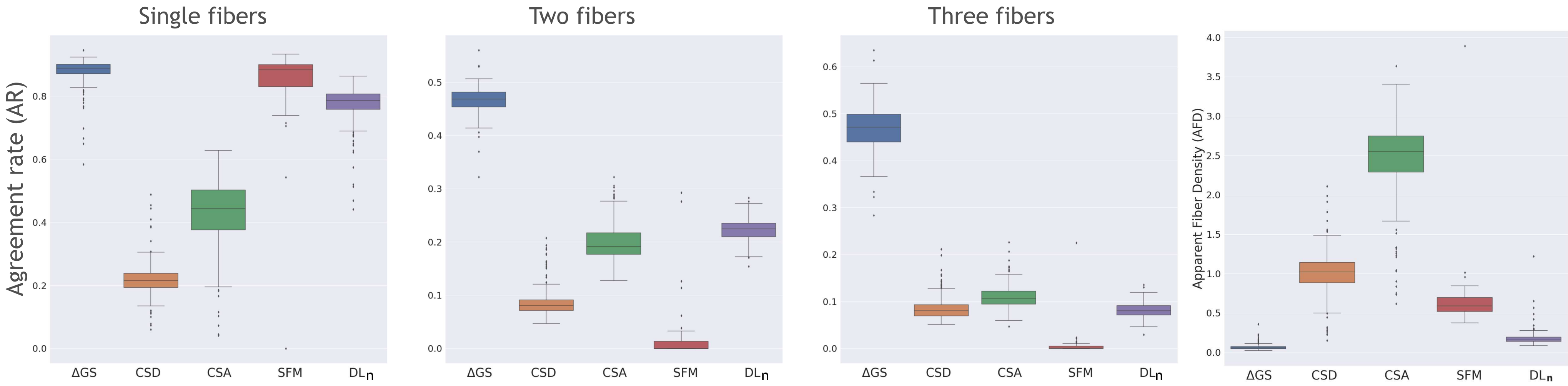


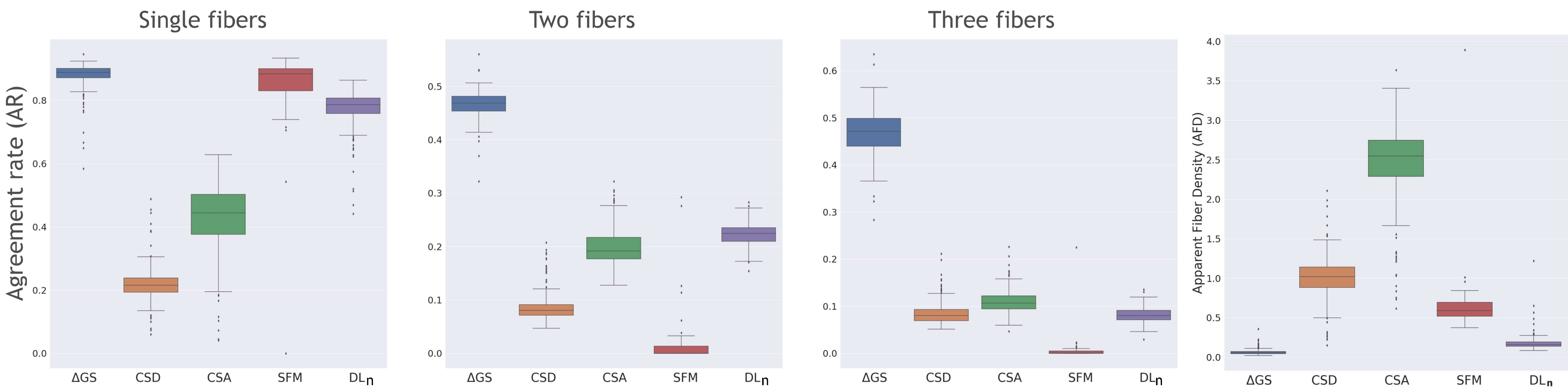
QUANTITATIVE RESULTS: DHCP NEWBORNS



Method	b-values (s/mm^2)	M	Angular error		
			Single fibers	Two fibers	Three fibers
DL_n	$\{0, 1000\}$	7	$10°(\pm 0.2)$	$20°(\pm 0.3)$	$30°(\pm 0.1)$
CSD	$\{0, 2600\}$	148	$7°(\pm 0.2)$	$16°(\pm 0.3)$	$27°(\pm 0.1)$
CSA	$\{0, 400, 1000, 2600\}$	300	$43°(\pm 0.3)$	$37°(\pm 0.1)$	$35°(\pm 0.1)$
SFM	$\{0, 400, 1000, 2600\}$	300	$42°(\pm 0.6)$	$37°(\pm 2.0)$	$35°(\pm 4.0)$
ΔGS	$\{0, 400, 1000, 2600\}$	150	$6°(\pm 0.1)$	$14°(\pm 0.1)$	$25°(\pm 0.1)$

- Low agreement rate within the ground truth for multiple fibers
- Our method with 7 diffusion measurements ~ other methods with x21 and x43 more measurements
- Lowest error for our method in approximating the apparent fiber density (AFD)

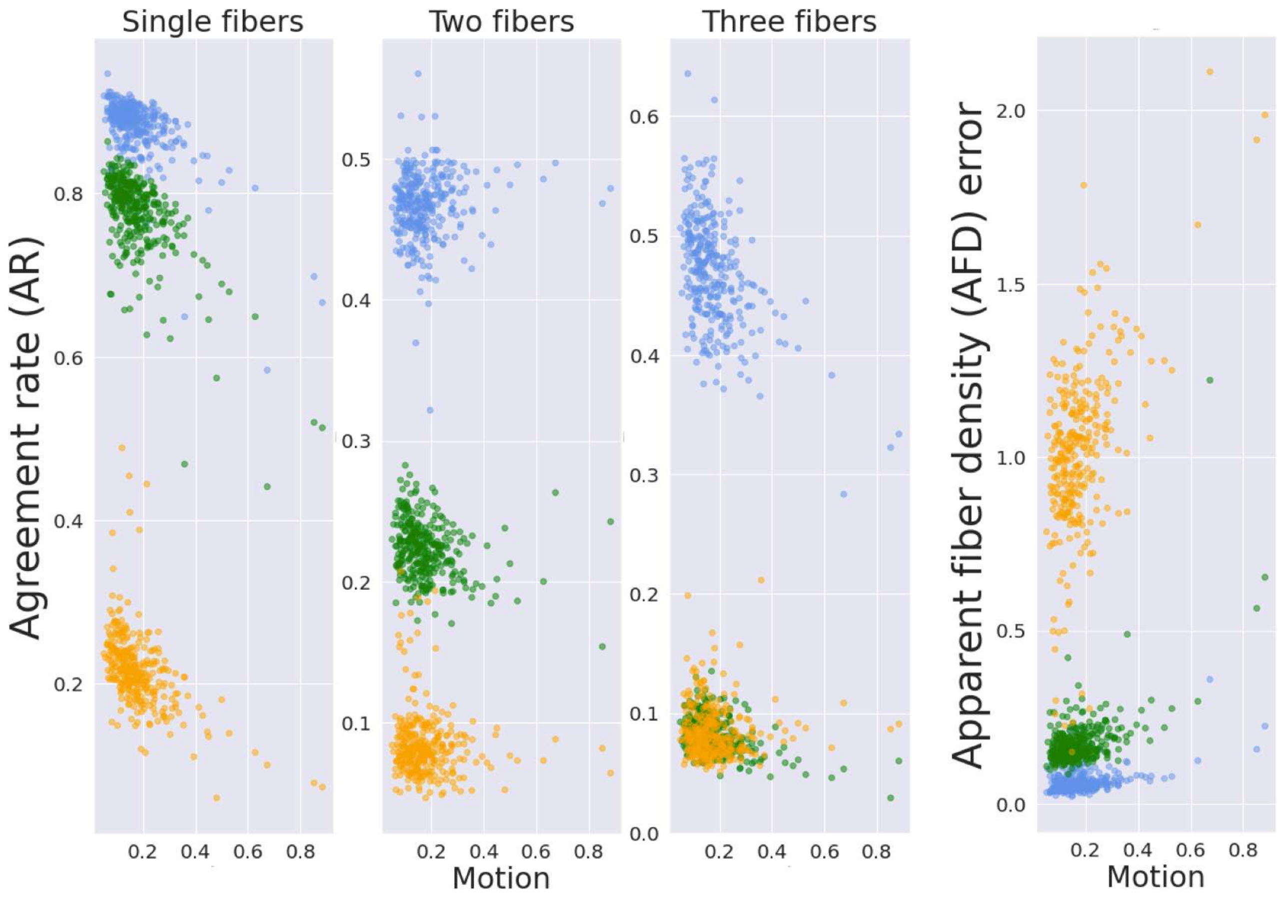
QUANTITATIVE RESULTS: DHCP NEWBORNS



Method	b-values (s/mm^2)	M	Agreement rate (Angular error)			AFD error
			Single fibers	Two fibers	Three fibers	
DL_n	$\{0, 1000\}$	7	77.5% (10°)	22.2% (20°)	8.0% (30°)	0.178 (±0.083)
MLP	$\{0, 1000\}$	7	74% (16°)	15.5% (28°)	7.7% (32°)	0.398 (±0.104)
CTtrack	$\{0, 1000\}$	7	74.5% (16°)	16.8% (25°)	4.4% (32°)	0.263 (±0.105)

- Low agreement rate within the ground truth for multiple fibers
- Our method with 7 diffusion measurements ~ other methods with x21 and x43 more measurements
- Lowest error for our method in approximating the apparent fiber density (AFD)
- DL also outperforming MLP & CTtrack

CORRELATION TO QUALITY CONTROL METRICS



		Single fibers	Two fibers	Three fibers	AFD error
●	ΔGS	r=-0.44/p=2e-16	r=+0.09/p=0.1	r=-0.41/p=3e-14	r=+0.34/p=6e-10
●	DL_n	r=-0.48/p=2e-20	r=-0.29/p=1e-07	r=-0.35/p=8e-11	r=+0.36/p=2e-11
●	CSD	r=-0.54/p=9e-26	r=-0.1/p=0.06	r=-0.1/p=0.08	r=+0.39/p=1e-12

- No correlation to other QC metrics (Outlier-ratio, SNR) and scan age
- Correlation to motion as estimated by SHARD pipeline[1]

[1] Christiaens et al., Neuroimage, 2021

UNCERTAINTY ESTIMATION

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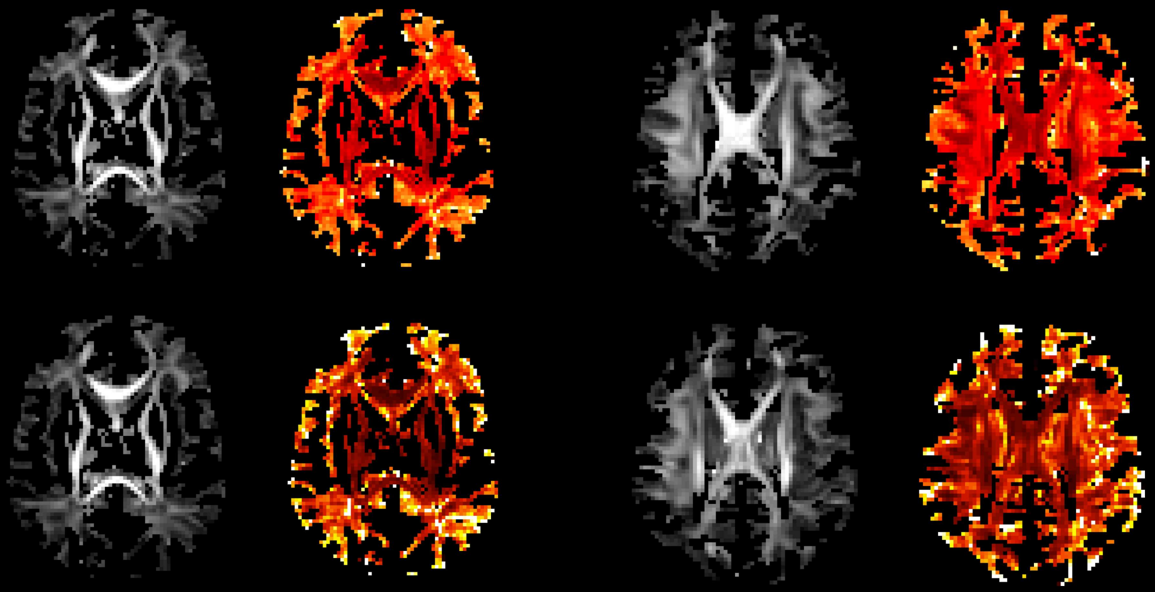
Subject 1

Subject 2



FA | Uncertainty map | FA | Uncertainty map

- Wild bootstrap uncertainty

$$\sigma = \frac{1}{N_{WBS}} \sum_{i=1}^{N_{WBS}} ||FOD_i - \mu||_2 \quad \text{where } \mu_c = \frac{1}{N_{WBS}} \sum_{i=1}^{N_{WBS}} FOD_{i,c} \quad \text{and } c \in \{1, 45\}$$

$$\sigma_{norm} = \frac{\sigma}{m_j} \qquad \text{where } m_j = \frac{1}{45} \sum_{c=1}^{45} ||FOD_{j,c}|| \quad \text{and } j \in \{1, N_{WBS}\}$$

Jones et al., MRM, 2003; Yuan et al., TMI, 2008; Jeong et al., MRM, 2008

QUALITATIVE RESULTS: CLINICAL NEWBORNS BCH

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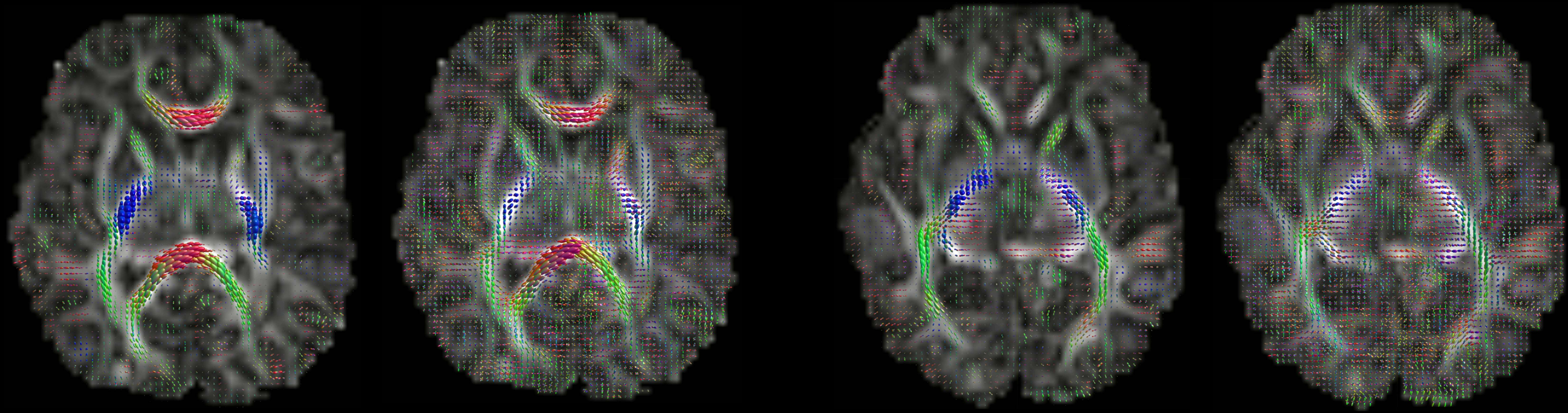
Slice 1 **Slice 2**



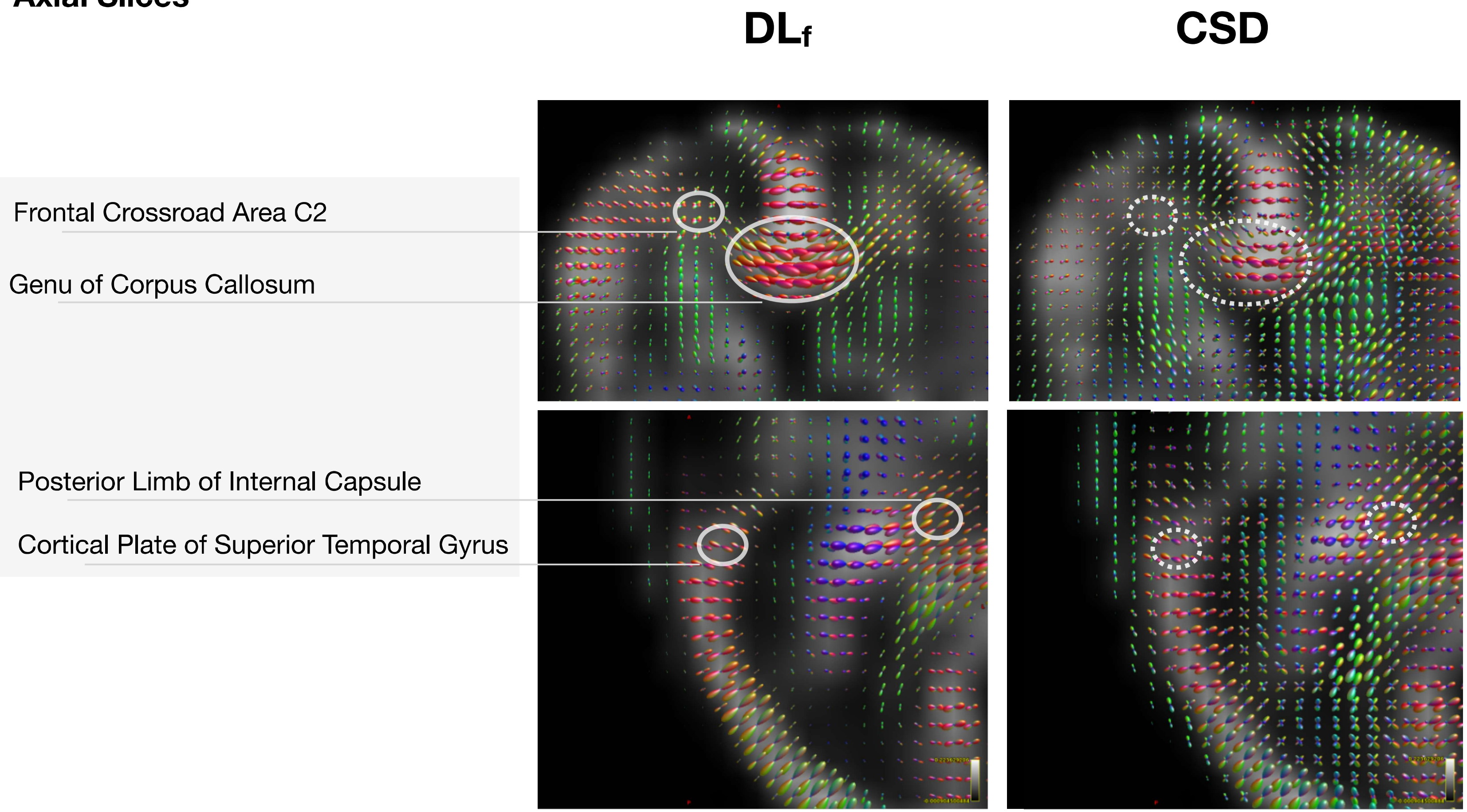
DL_n CSD DL_n CSD

DL_n using 7 measurements

CSD using 35 measurements

FETAL EVALUATION

Axial Slices

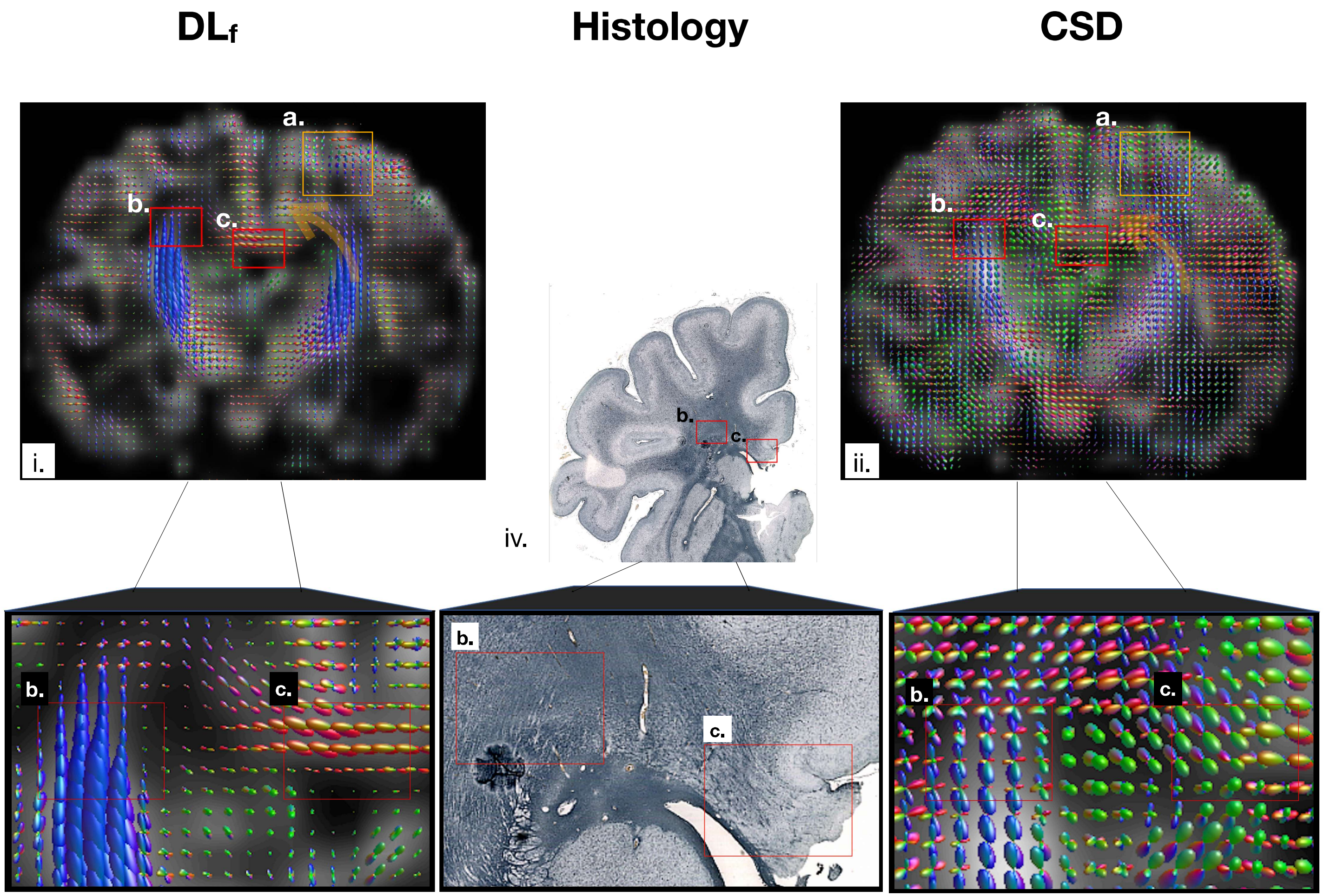


[1] Karimi et al., Neuroimage, 2021

Regions of interests (ROIs) definition based on histology and immunohistochemistry as in previous works[1]

FETAL EVALUATION

Coronal Slices



Regions of interests (ROIs) definition based on histology and immunohistochemistry as in previous works[1]

[1] Karimi et al., Neuroimage, 2021

FETAL EVALUATION: RESULTS

Fetal brain region	DL_f	Tied	CSD
Frontal crossroad region	10	0	1
Genu of corpus callosum	11	0	0
Cortex of Insula	2	5	4
Posterior limb of internal capsule	7	2	2
Cortex of superior temporal gyrus	6	2	3
Subplate of the precentral gyrus	4	0	7
Internal capsule	3	0	8
Cerebral peduncles	1	1	9
Intermediate zone, genuculocortical	4	3	4
Intermediate zones, callosal	10	0	1
Prefrontal subplate	6	4	1
Prefrontal cortical plate	8	2	1
Count per ROI	**7**	**1**	**3**
Count per subject	**9**	**0**	**2**

GENERALIZABILITY & DOMAIN SHIFTS

Features	Baby Connectome Project (BCP)
Number of Subjects	210
Age Span	1-5 years
Imaging Device	3T Siemens Magnetom Prisma
Resolution	1.5 × 1.5 × 1.5 mm^3
B-values	{0, 500, 1000, 1500, 2000, 2500, 3000} s/mm^2

- Assessing the performance of deep learning on a different dataset
- Generalization from one dataset to another

DOMAIN SHIFT IMPACTS

CROSS-AGE AND CROSS-SITE DOMAIN SHIFT IMPACTS ON DEEP LEARNING-BASED WHITE MATTER FIBER ESTIMATION IN NEWBORN AND BABY BRAINS

Rizhong Lin [1,2,3] *Ali Gholipour* [4] *Jean-Philippe Thiran* [1,2,5] *Davood Karimi* [4]
Hamza Kebiri [2,5,⋆] *Meritxell Bach Cuadra* [5,2,⋆]

[1] Signal Processing Laboratory 5 (LTS5), École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
[2] Department of Radiology, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland
[3] College of Electronic and Information Engineering, Tongji University, Shanghai, China
[4] Computational Radiology Laboratory, Department of Radiology,
Boston Children's Hospital and Harvard Medical School, Boston, MA, USA
[5] CIBM Center for Biomedical Imaging, Switzerland

Lin et al., ISBI *2024*

https://arxiv.org/abs/2312.14773

DISCUSSION

- Conclusion
  - Deep learning can achieve state-of-the-art results in ODF estimation with fewer measurements
  - Can have a big impact on scan time reduction
  - Low agreement for multiple-fiber voxels within the dataset
  - Deep learning can provide some level of generalization across centers/ protocols and anatomies (i.e. fetuses)

- Limitations
  - Specific response functions learning
  - Generalization to pathological subjects
  - Tractography ?

Through-Plane Super-Resolution With Autoencoders in Diffusion Magnetic Resonance Imaging of the Developing Human Brain

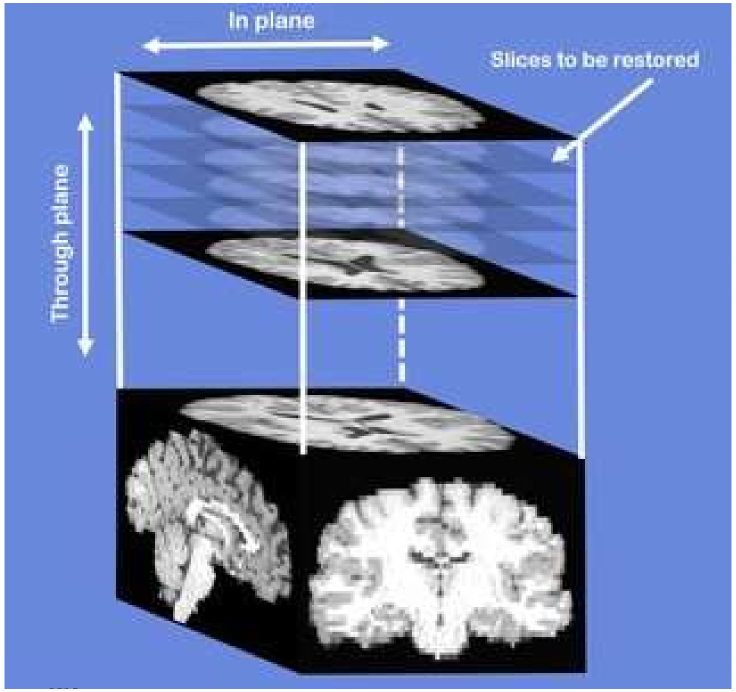
Hamza Kebiri[1,2]*, *Erick J. Canales-Rodríguez*[3], *Hélène Lajous*[1,2], *Priscille de Dumast*[1,2], *Gabriel Girard*[1,2,3], *Yasser Alemán-Gómez*[1], *Mériam Koob*[1], *András Jakab*[4,5] *and Meritxell Bach Cuadra*[1,2,3]

[1] Department of Radiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [2] CIBM Center for Biomedical Imaging, Lausanne, Switzerland, [3] Signal Processing Laboratory 5 (LTS5), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, [4] Center for MR Research University Children's Hospital Zurich, Zurich, Switzerland, [5] Neuroscience Center Zurich, University of Zurich, Zurich, Switzerland

Kebiri et al., ISMRM *2022*; *Frontiers in Neurology, 2022*

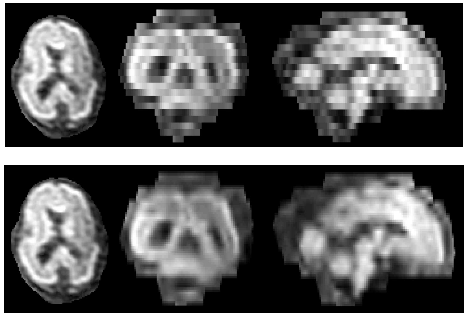
https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2022.827816/

THROUGH-PLANE RESOLUTION



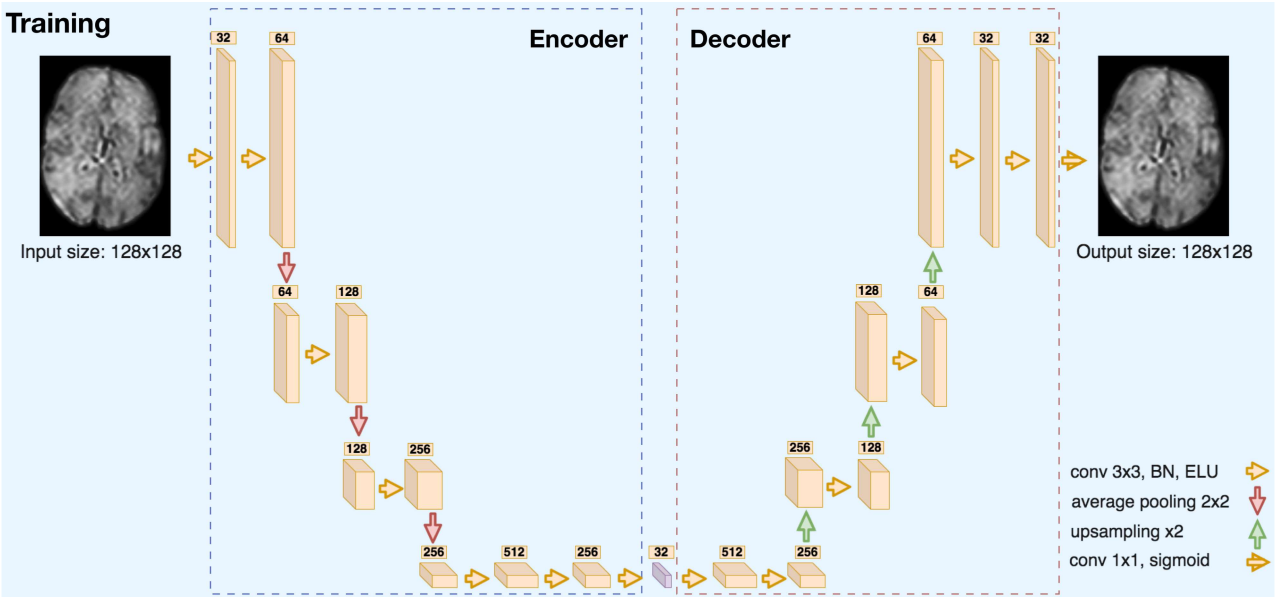
Adapted from Chai et al., IEEE Access, 2020

- Interpolation
  - Typically performed in low-through-plane resolution series in dMRI of developing brains
  - Interpolation was shown to be beneficial in dMRI of adult brains[1]



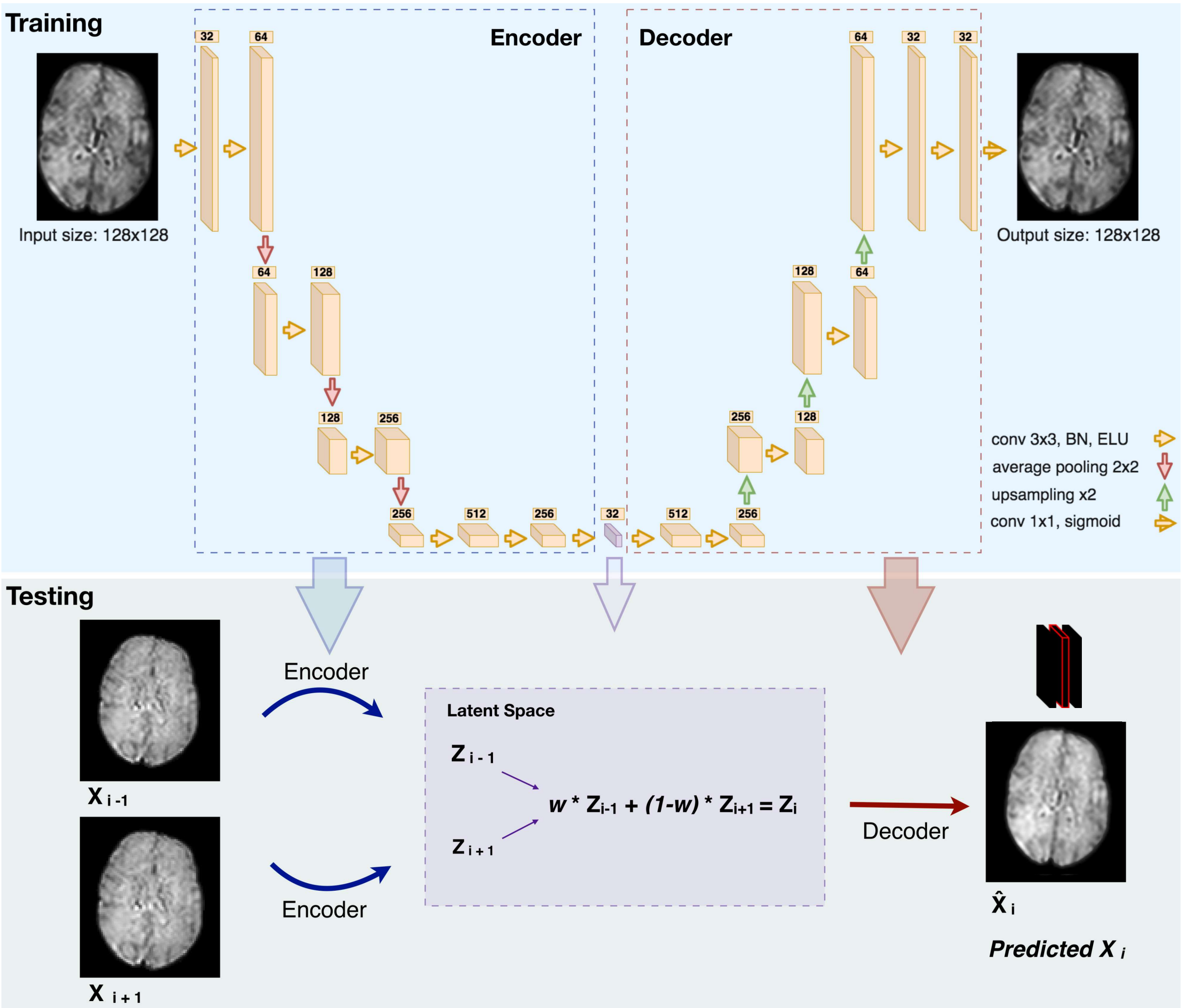
[1]Dyrby et al., Neuroimage 2014

MODEL ARCHITECTURE



Sander et al., SPIE Medical Imaging 2021

MODEL ARCHITECTURE & INFERENCE



DATA

- PRE-TERM
  - 31 subjects
  - Gestational age: 29-37 weeks
  - 25,920 slices of *1.17 x 1.17 mm²*
  - Slice thickness: *1.5 mm*
  - b = 1000 s/mm²
- FETAL
  - 6 subjects (3 with motion)
  - Gestational age: 23-35 weeks
  - In-plane: *1 x 1 mm²*
  - Slice thickness: *4-5 mm*
  - b = 700 s/mm²

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Developing Human Connectome Project

UNIVERSITÄTS-KINDERSPITAL ZÜRICH
Das Spital der Eleonorenstiftung

RAW SIGNAL MEAN SQUARED ERROR

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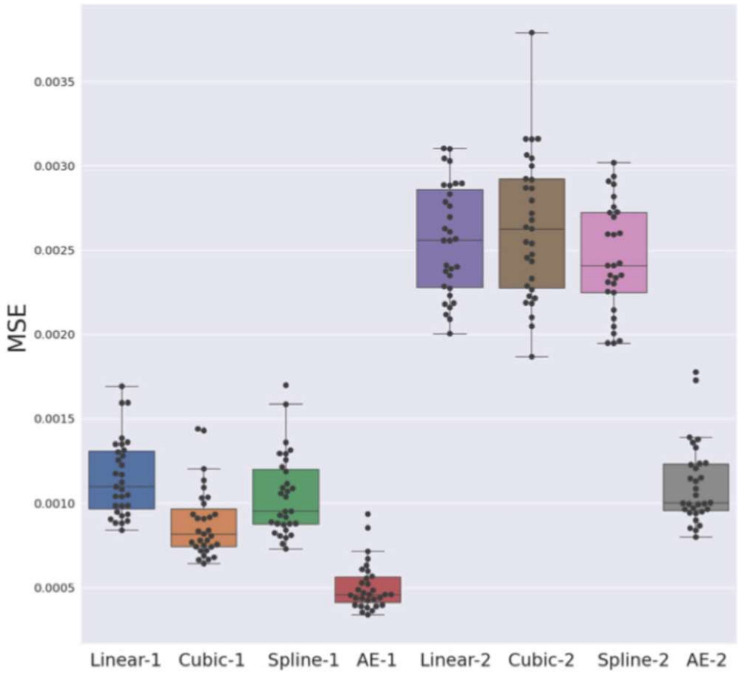
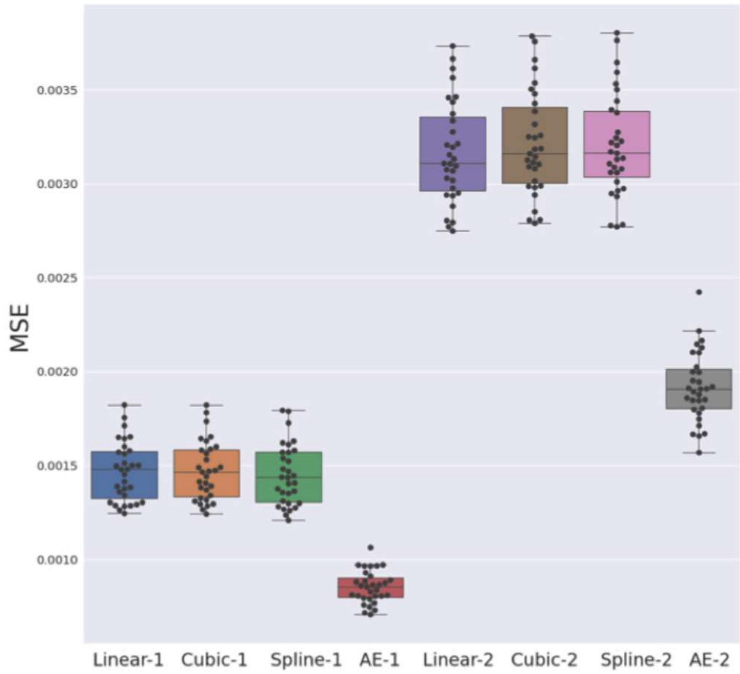
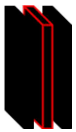
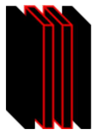
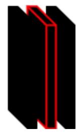
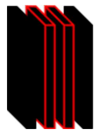
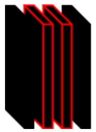
b0



b1000



- Autoencoder outperforming interpolations
- Higher gap for 

DWI LATENT SPACE EXPLORATION

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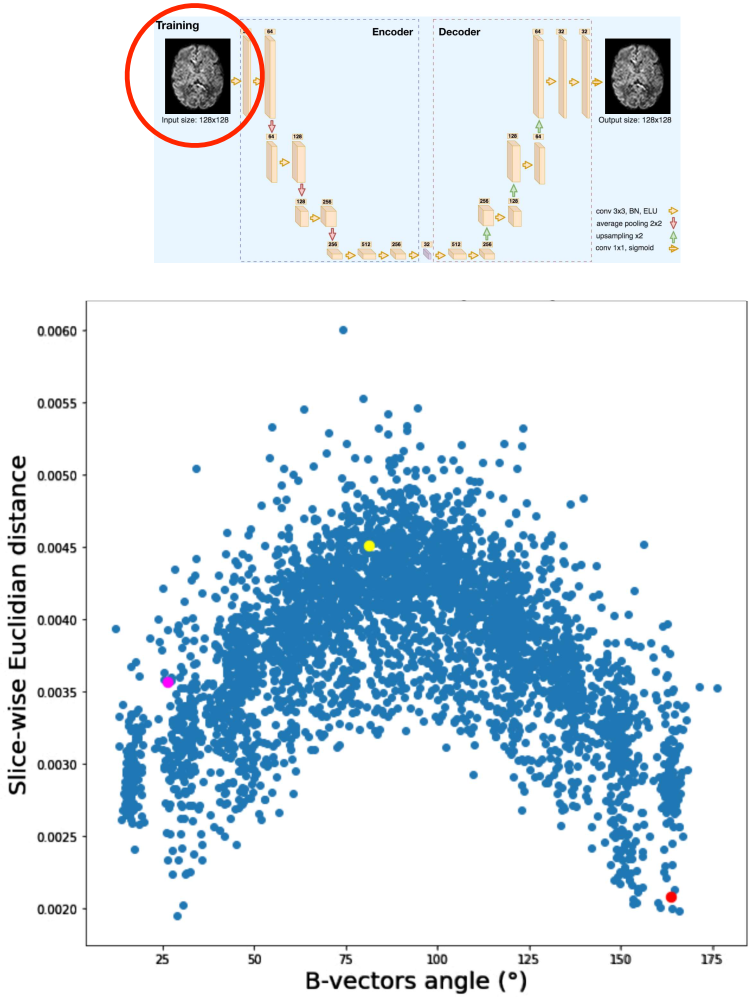
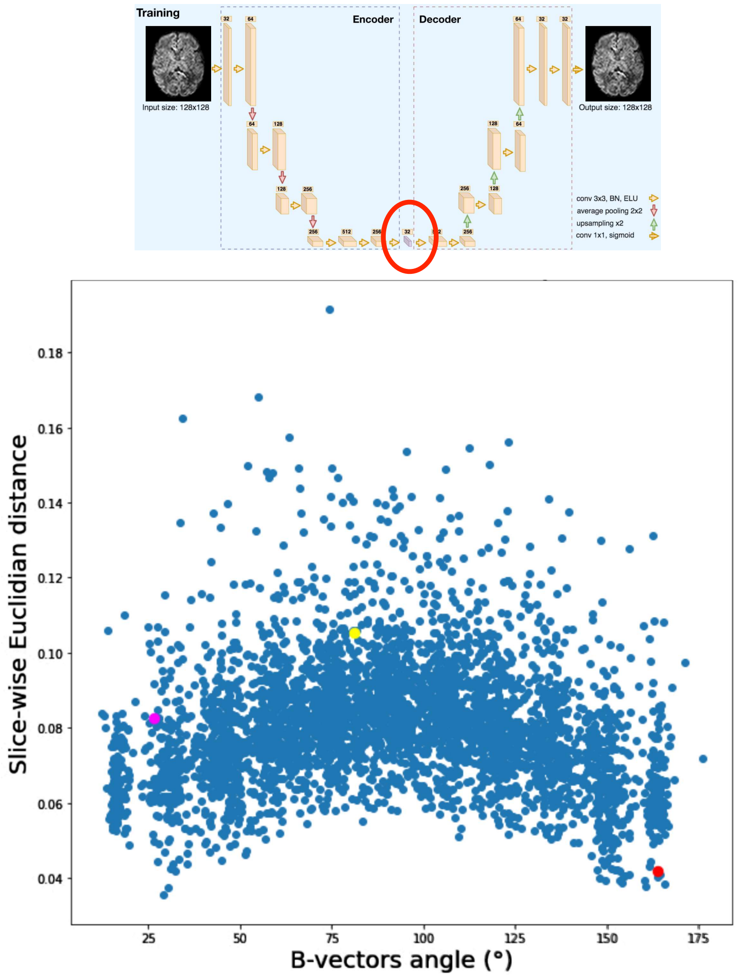
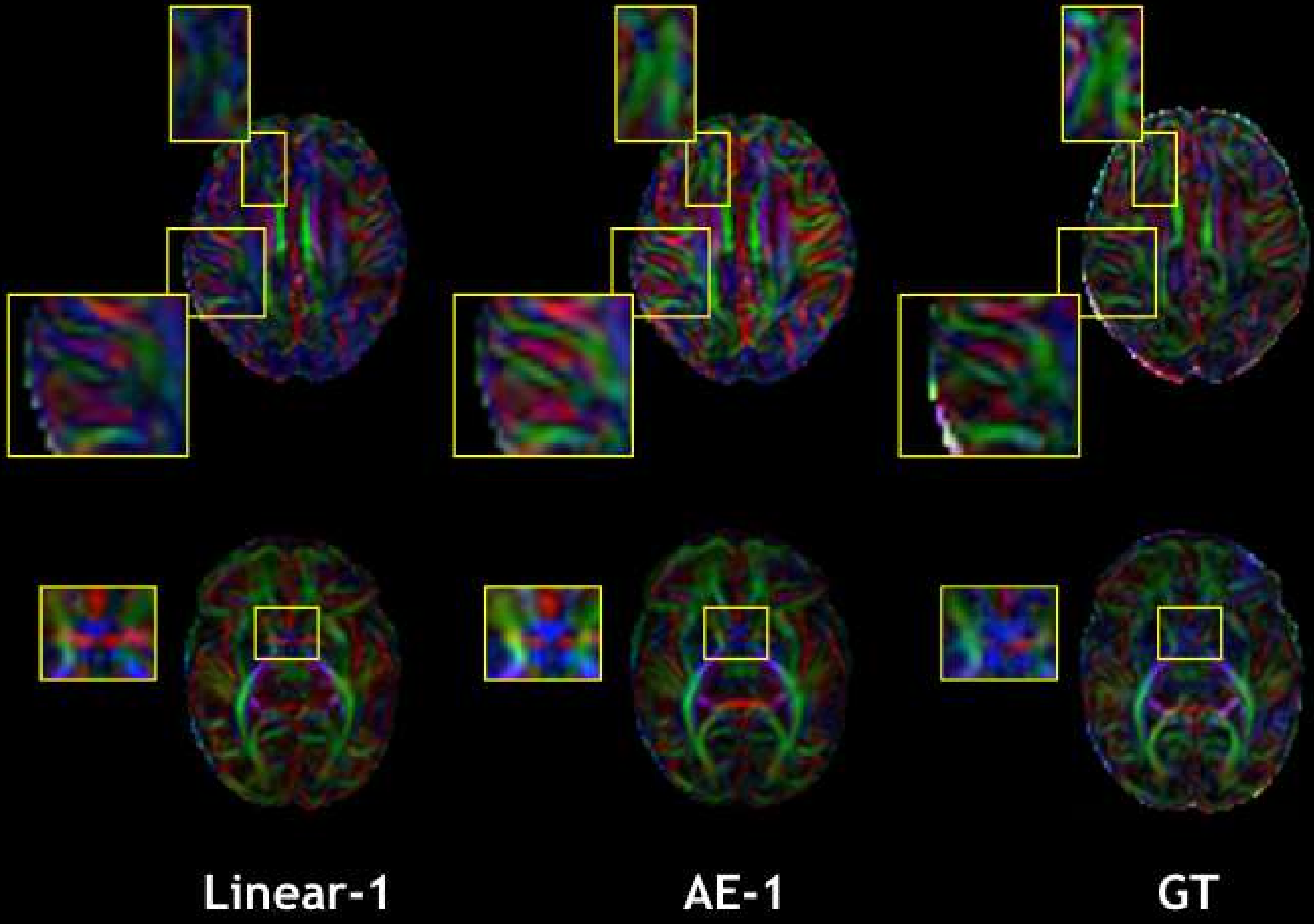
- Distance between all B1000 volumes & between their encodings

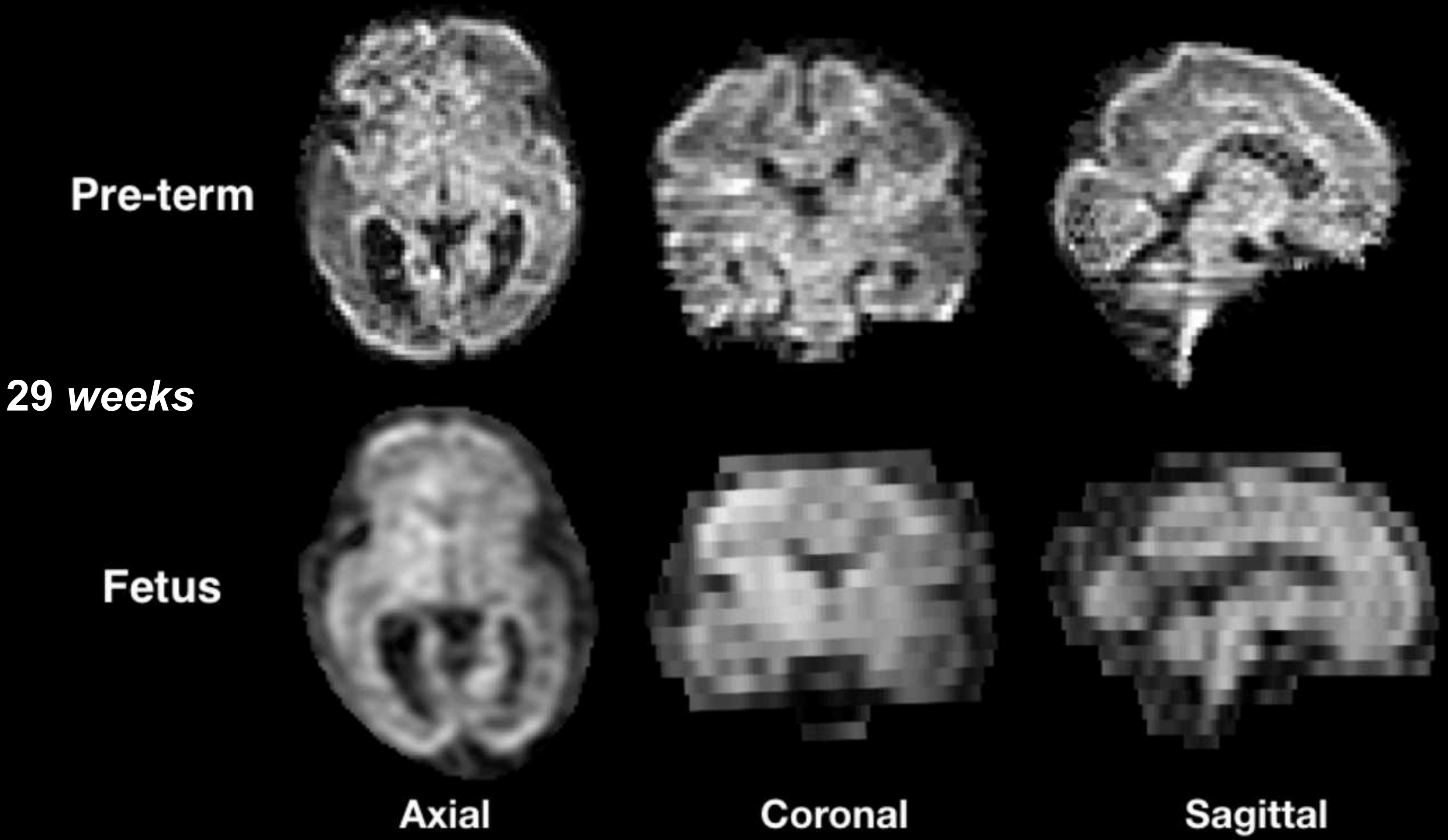




PRE-TERM QUALITATIVE RESULTS: COLOR FA

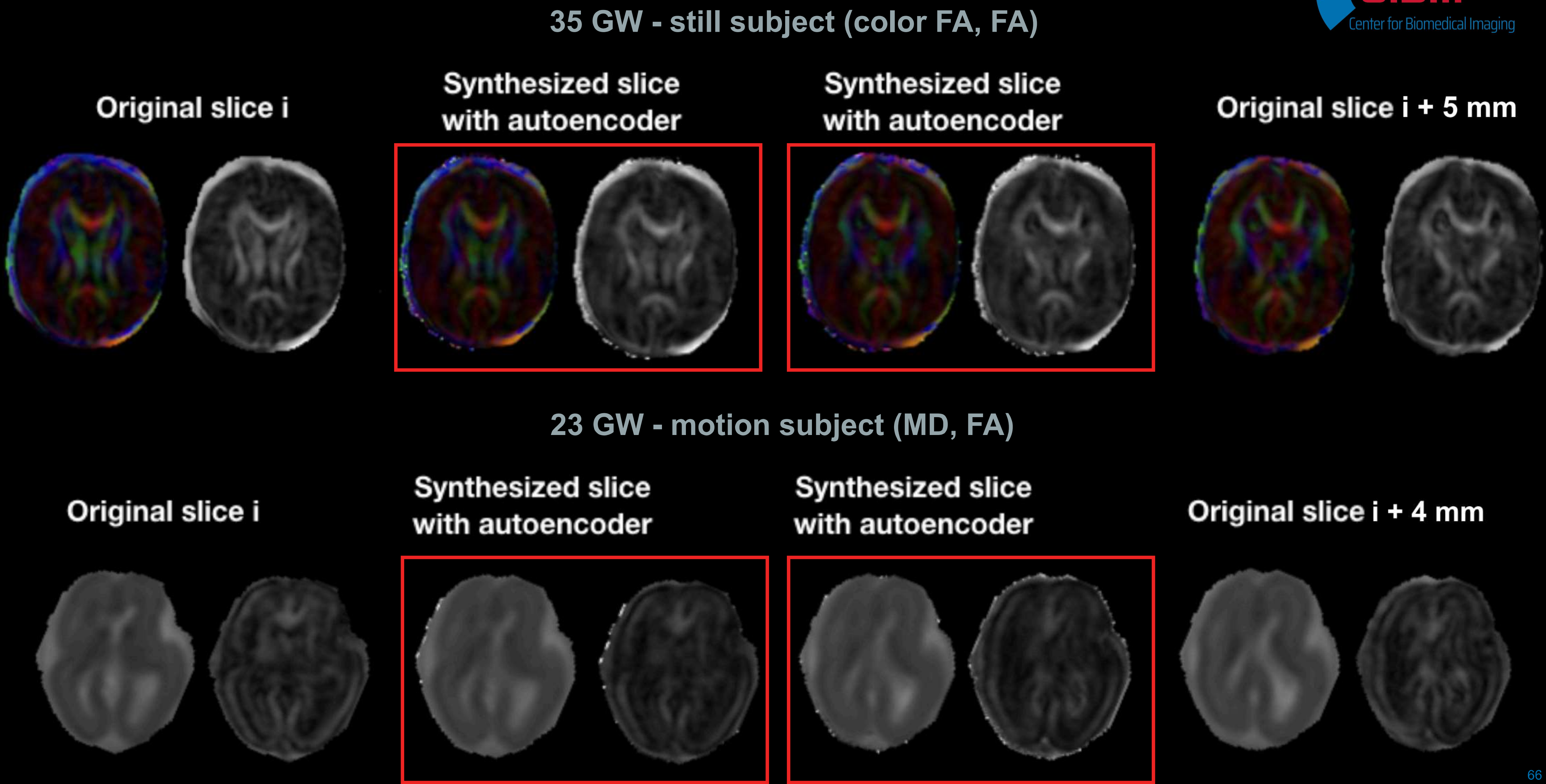


ANATOMICAL SIMILARITY PRE-TERM & FETAL SUBJECTS



Pre-term subject from dHCP data (Hutter et al., MRM, 2018; Tournier et al., NMR in Biomedicine, 2020)

QUALITATIVE FETAL RESULTS: DTI MAPS



DISCUSSION

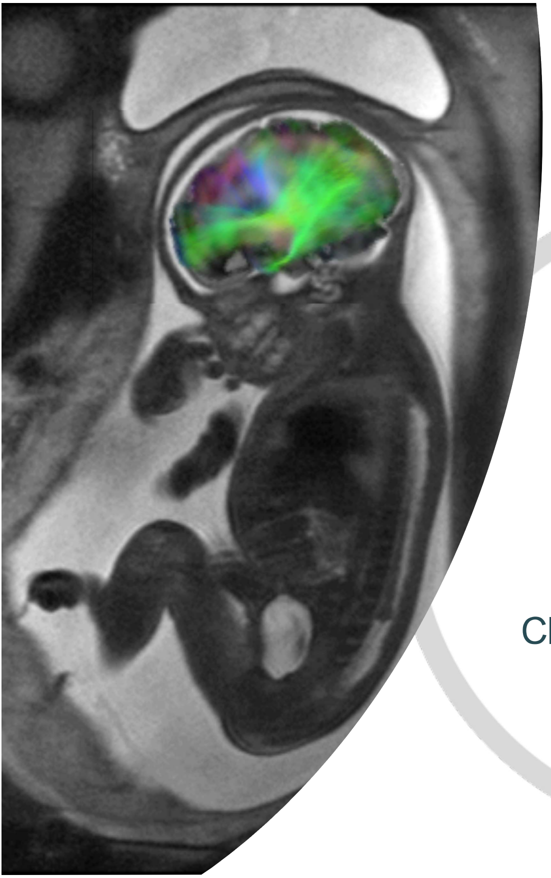
- Conclusions
  - Autoencoders can be used for dMRI super-resolution and outperform conventional interpolations
  - They can also be used in slice outlier recovery
  - Training on b0 images can generalize to gradient diffusion volumes
  - Generalizing from pre-term newborns to fetal might be possible

- Limitations
  - Shallow fetal evaluation
  - Autencoders generate smooth outputs (similarly to interpolation methods)
  - Potential network hallucinations
  - Motion

Conclusion

DISCUSSION

- Conclusion
  - Overview on medical imaging tools with a focus on MRI
  - Introduction to machine learning and its applications to medical imaging
  - Two examples of supervised and unsupervised learning approaches on medical imaging tasks
- Future directions of ML in medical imaging (MRI)
  - Domain shift issues (training and testing on different machines/protocols/ages/etc.)
  - AI hallucinations
  - Reproducibility/variability
  - Clinical translations
  - More (publicly available) data needed (synthetic data?)
  - Multi-modal large language models (LLMs)



THANK YOU!

Boston Children's Hospital
Until every child is well™

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Thank you for your attention

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