Pediatric Neuroradiology:
Biomarker Challenges and Opportunities

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Boston Children's Hospital

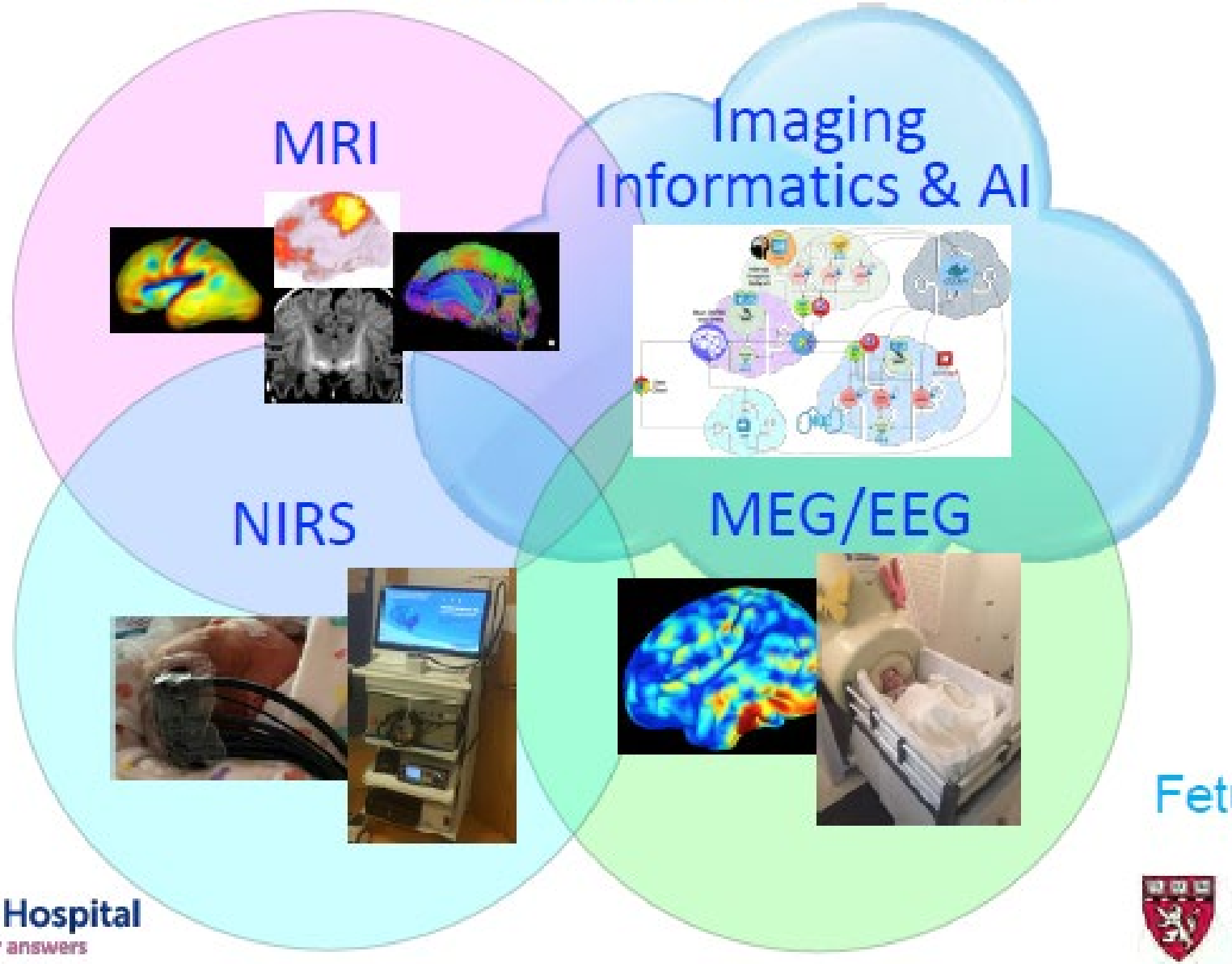
Disclosures

Aspect Imaging, consultant

TracInnovations, collaboration

SyMRI, collaboration

Fetal Neonatal Neuroimaging and Developmental Science Center (FNNDSC)



> $40M in active funding

Non-significant Risk Devices

March 2023:

15 Faculty
7 Post Docs
3 Admin
16 Research Staff
26 Student Interns

Fetus, Infant, Toddler

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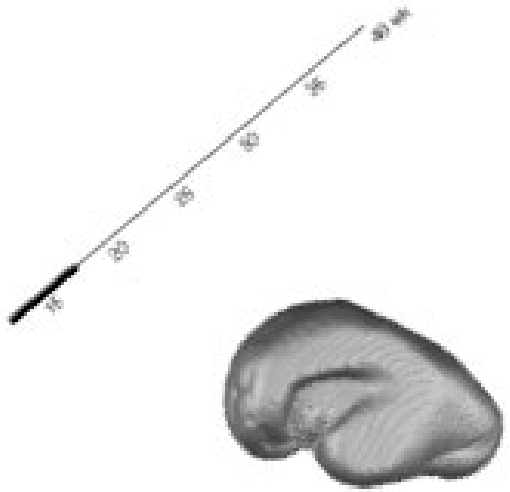
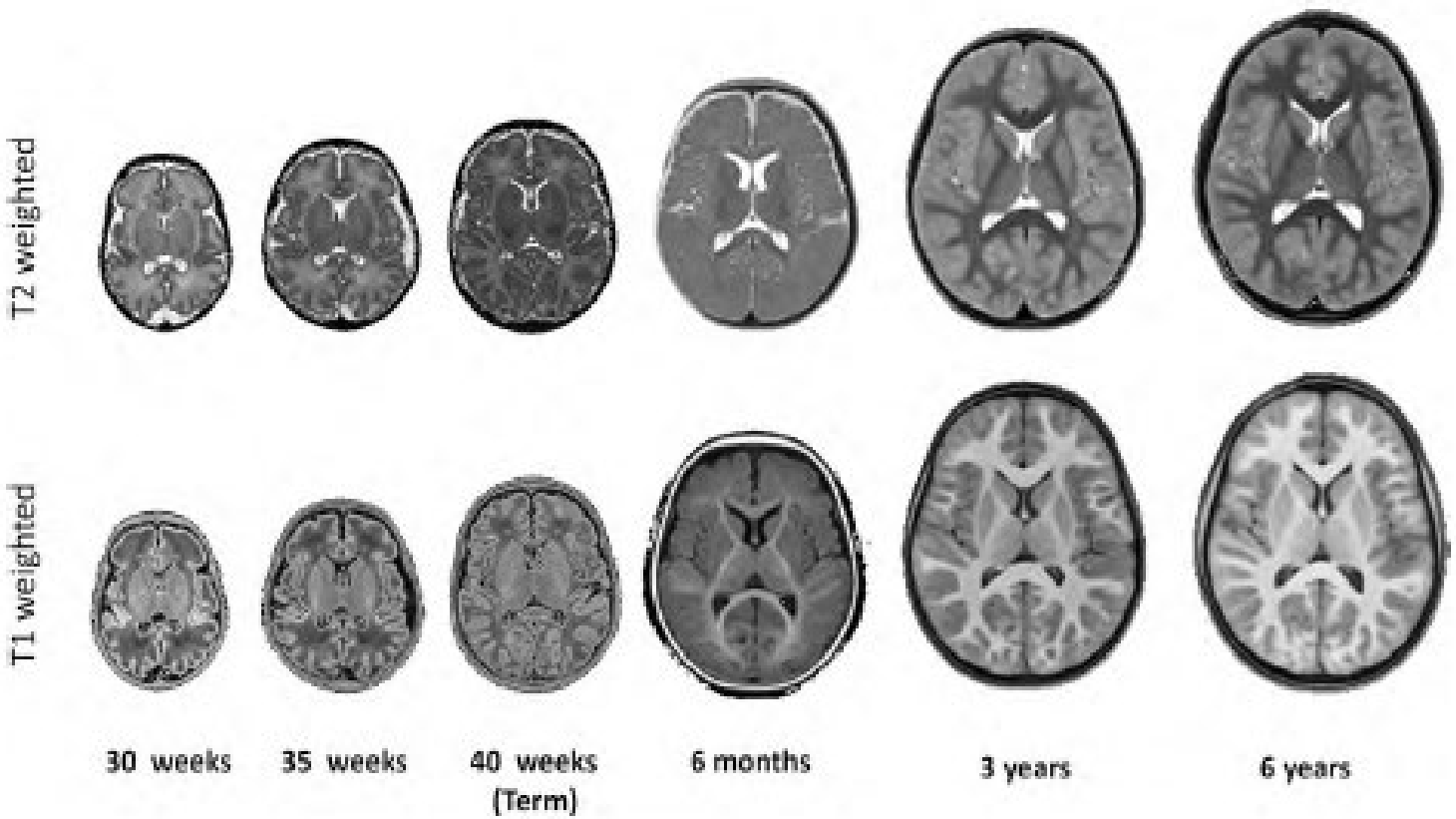
Rapid Growth and Development



Lana Vasung,
MD PhD



Batalle *et al.* J Child Psychol Psychiatr 2017

Biomarkers for Lesion Detection, Outcome Prediction

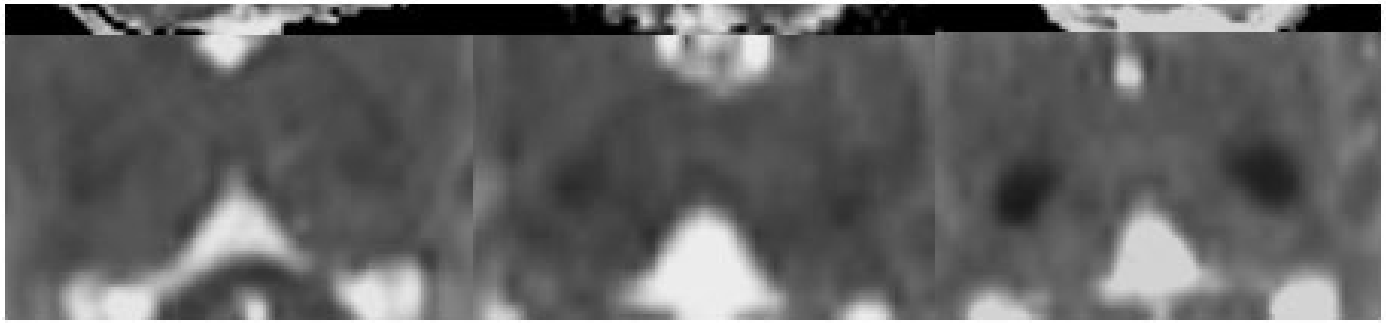
ADC Maps

Injury peaks at different days in different babies

- Need to determine optimal day for prediction based on multiple factors

20-40% disagreement between readers Goergen et al. Clinical Radiology 2014.

- Need consensus reads/training
- Expensive, time consuming and impossible to translate to clinical practice

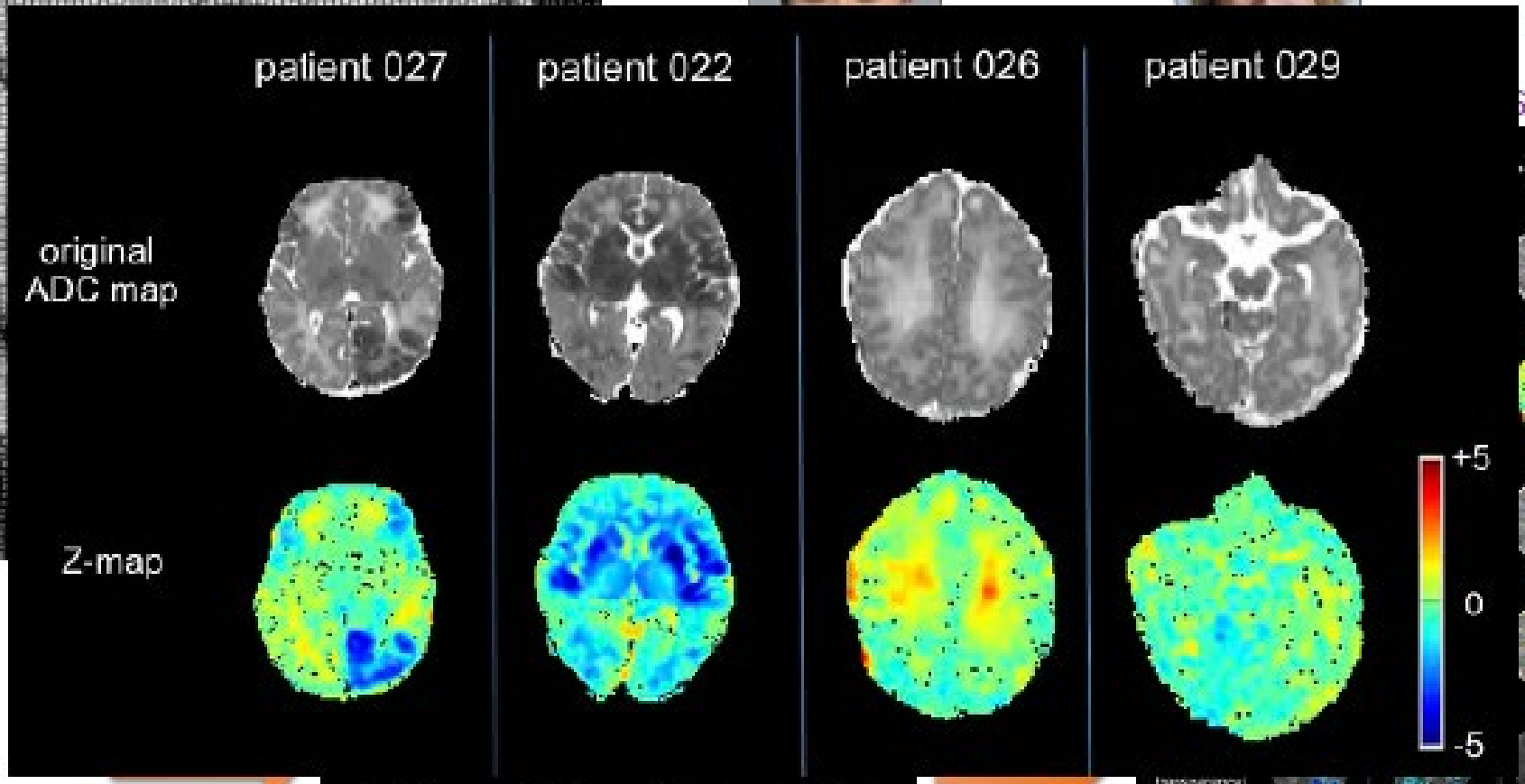


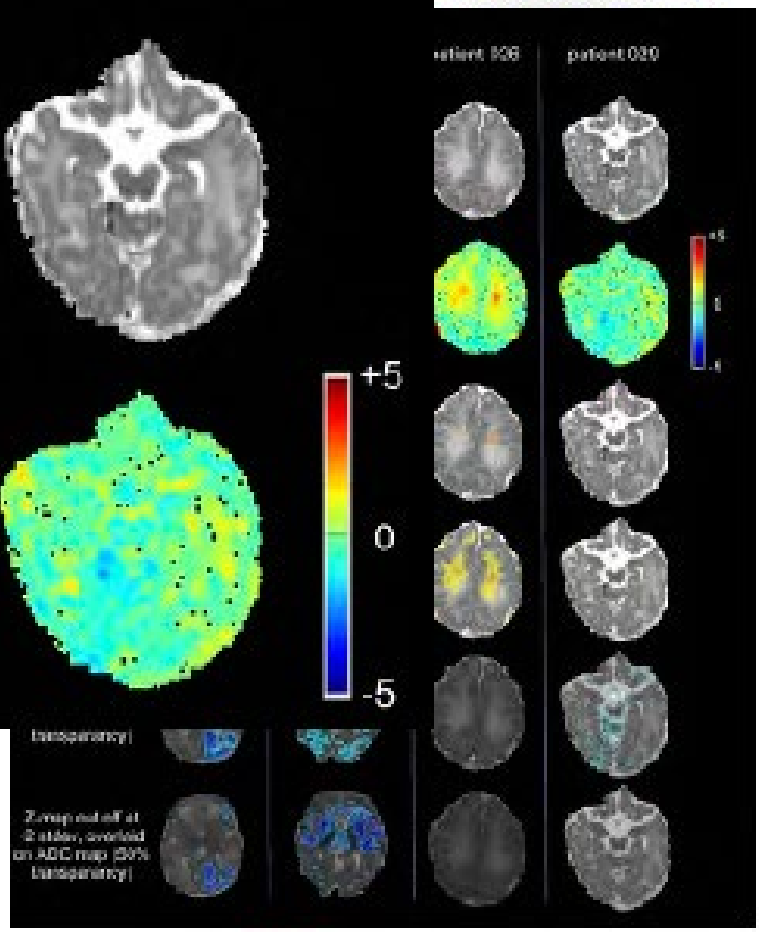
Neonate 1 Neonate 2 Neonate 3

- RCT of new treatments for neonatal Hypoxic Ischemic Injury use qualitative scoring of single time point MRI (4 – 10 days) as an early outcome measure

Biomarkers for Lesion Detection, Outcome Prediction

Susan Sotardi MD





R61NS126792 Grant, Laptook, Ou
R01EB014947 Murphy, Gollub, Grant

Sotardi et al, *Radiology* 2021
Ou et al, *NeuroImage* 2016
Ou, et al, *HBM* 2017

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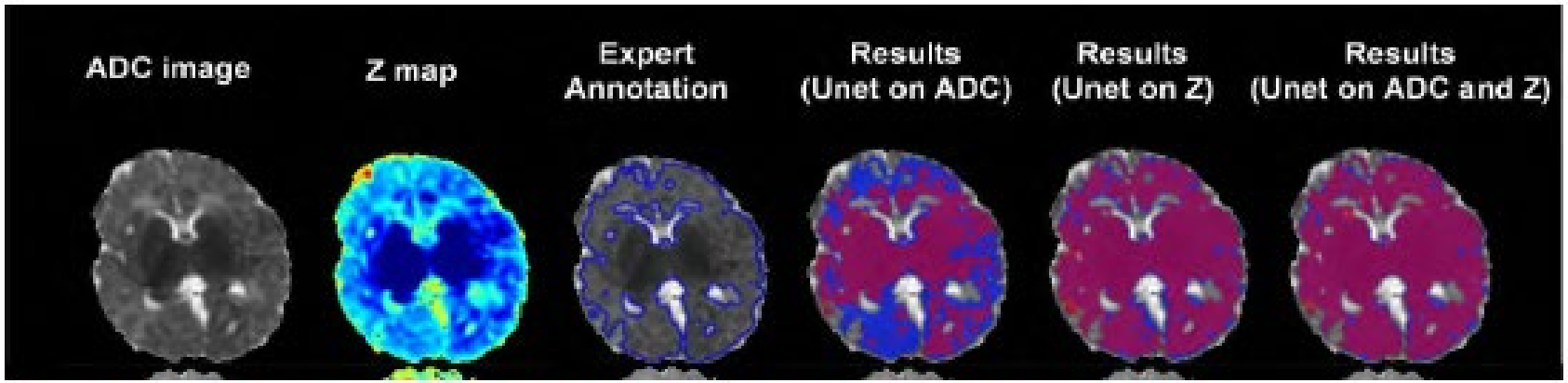
Biomarkers for Lesion Detection, Outcome Prediction



Yangming Ou PhD

R61 will gather ~ 430 MRI+* data sets from NRN
R21 will release ~ 202 MRI+ data sets from MGH/BCH
MICCAI competition for lesion detection approved
Goal: Robust lesion detection, optimal MRI timing for outcome prediction for use in RCT and in clinical practice

*EEG reads, clinical data elements
NRN = Neonatal Research Network

Zhang, ..., Grant, Ou; *under review*, 2023

R61NS126792 Grant, Laptook, Ou
R21NS121735 Ou

Comparison with the state-of-the-art
Dice=0.52 by Murphy, ..., de Vries, et al; 2017
Dice=0.82 by us; 2022

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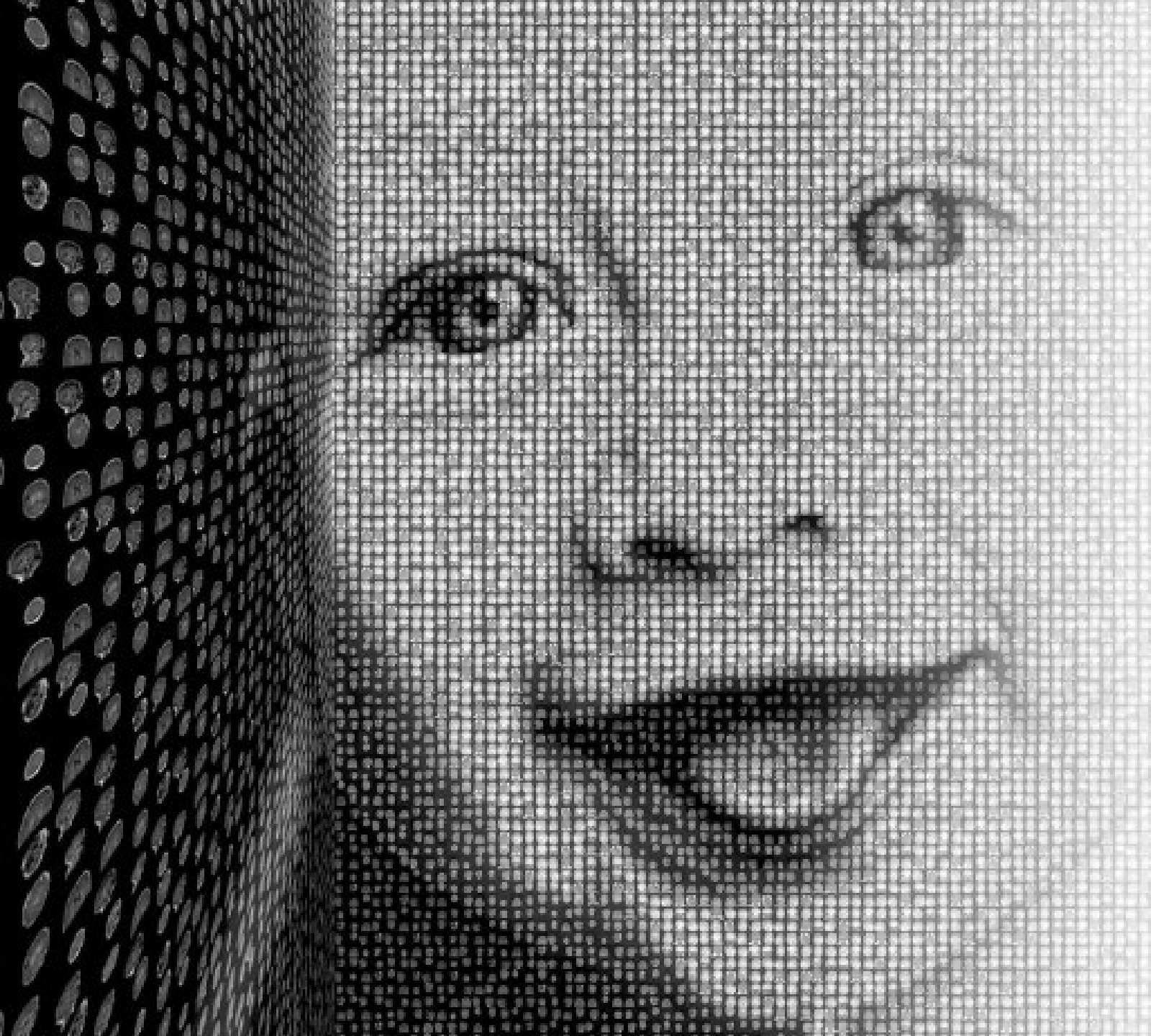


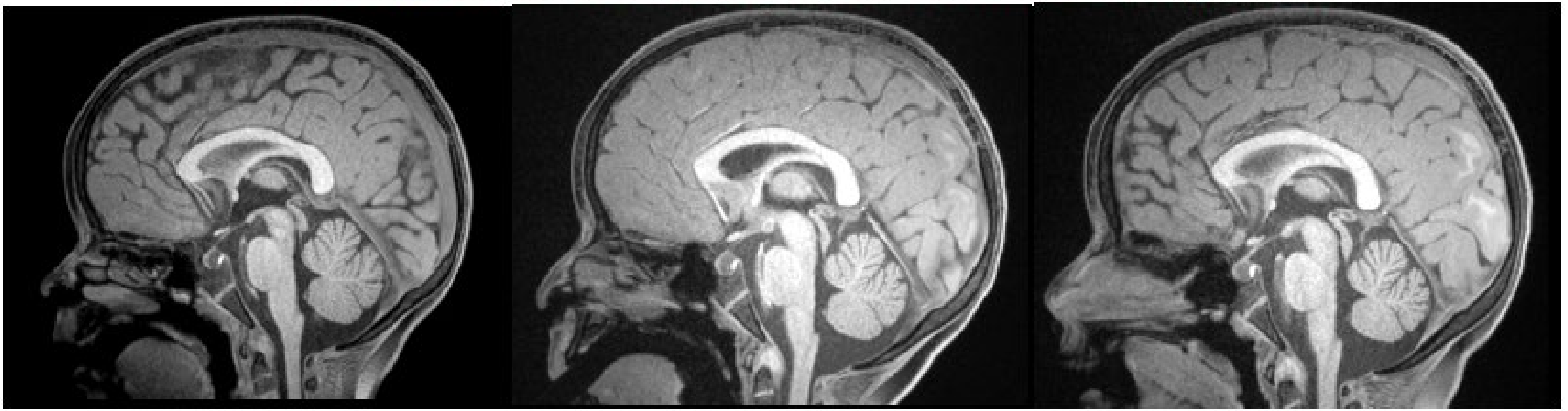
Can We Leverage Clinical Volumes?

- BCH does > 12,000 brain MRIs per year
- If all major pediatric hospitals standardized 1 - 3 sequences and shared data…

Engaging clinical imaging societies such as ASPNR, SPR, RSNA, ACR could make this happen…

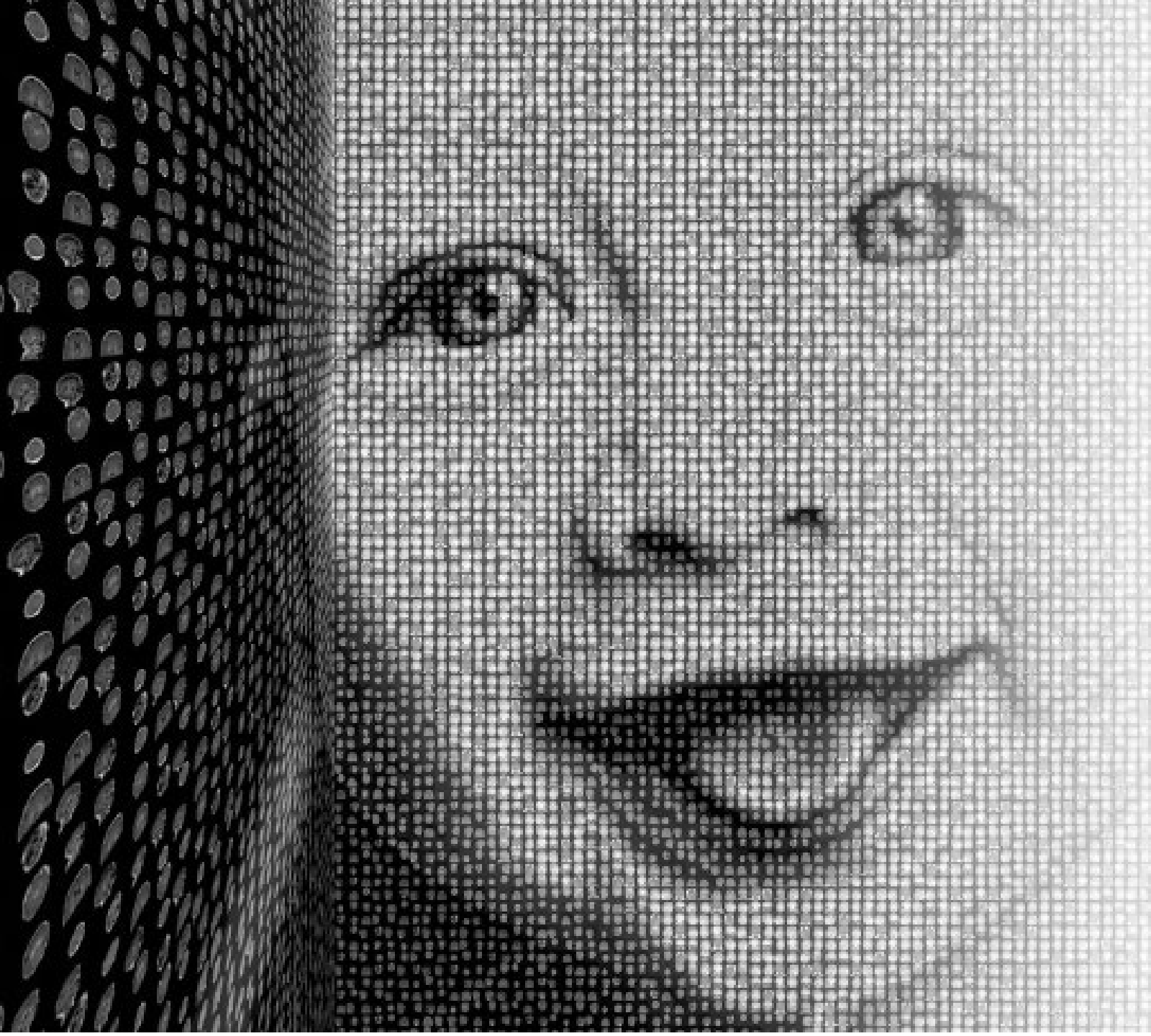
Non-lesional Biomarkers, Outcome Prediction

Investigational ASO treatment for an Ataxia Telangectasia



Baseline at 2.5 yrs | Follow up at 3.75 yrs | Follow up at 5.42 yrs

- Pediatric disorders often rare any many have bespoke treatments
- No guidelines for imaging and no easy to access to pediatric imaging databases to compare



Can we Leverage Public Datasets?

- Downloaded and curated >36,000 brain MRIs and data elements from >11 studies worldwide for lifespan project (0–100y)
  - ~ 400 aged 0-5y
- HBCD gathering ~7,000 longitudinal datasets 0-5y

Need to provide guidelines to sites doing clinical trials to match these acquisitions…

Non-lesional Biomarkers, Outcome Prediction

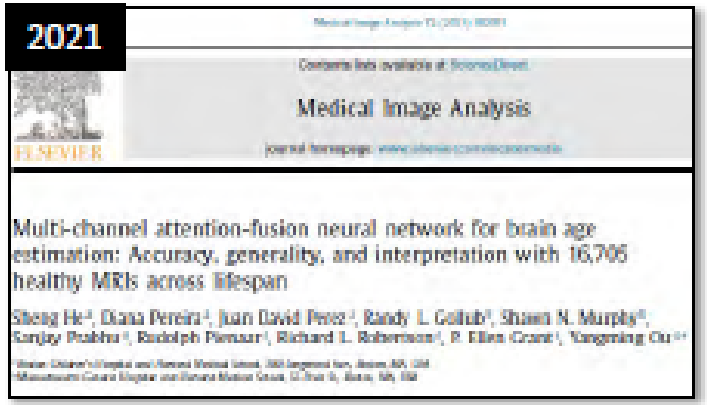
Brain Age Estimation

	$N_{samples}$	Age range [Median]	Male/Female
MGHBCH (He et al., 2020)	428	0–6 [1.7]	226/202
NIH-PD (Evans et al., 2006)	1211	0–22.3 [9.8]	585/626
ABIDE-I (Di Martino et al., 2014)	567	6.47–56.2 [14.8]	469/98
BGSP (Holmes et al., 2015)	1570	19–53 [21]	665/905
BeijingEN	180	17–28 [21]	73/107
IXI	556	20.0–86.3 [48.6]	247/309
DLBS (Park et al., 2012)	315	20–89 [54]	117/198
OASIS-3 (LaMontagne et al., 2018)	1222	42–97 [69]	750/472
ABCD (Volkow et al., 2018)	8639	9–11 [9.91]	4508/4131
CMI (Alexander et al., 2017)	1765	5–21.9 [10.1]	1117/648
CoRR (Zuo et al., 2014)	252	6–60 [20.4]	148/104
	16,705	0–97 years	8905/7800

Method	MAE (years)			
	Axial	Coronal	Sagittal	Fusion
ResNet18 [20]	3.45±0.17	3.38±0.07	3.87±0.10	3.25±0.09
BagNet-ResNet18 [19]	5.13±0.21	6.29±0.81	5.57±0.17	5.46±0.34
VGG [36]	3.48±0.16	3.29±0.09	3.67±0.13	3.11±0.12
BagNet-VGG [19]	4.08±0.09	5.87±0.25	5.11±0.32	4.75±0.19
Global-Transformer [38]	3.97±0.26	5.39±0.71	5.34±0.22	4.11±0.29
Local-Transformer [22]	3.50±0.10	3.32±0.10	3.78±0.13	3.28±0.03
Global-Local Transformer	**2.87±0.11**	**2.97±0.07**	**3.14±0.02**	**2.70±0.03**

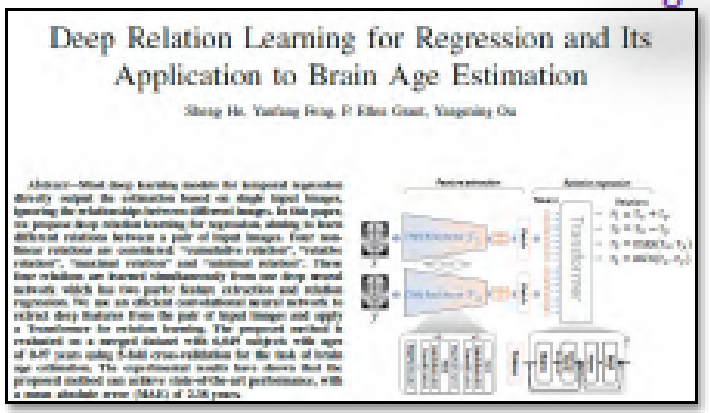
Yangming Ou PhD

Sheng He PhD



He et al, ISBI 2020; He et al, Med Image Ana 2021

He et al, IEEE TMI 2022a



He et al, IEEE TMI 2022b

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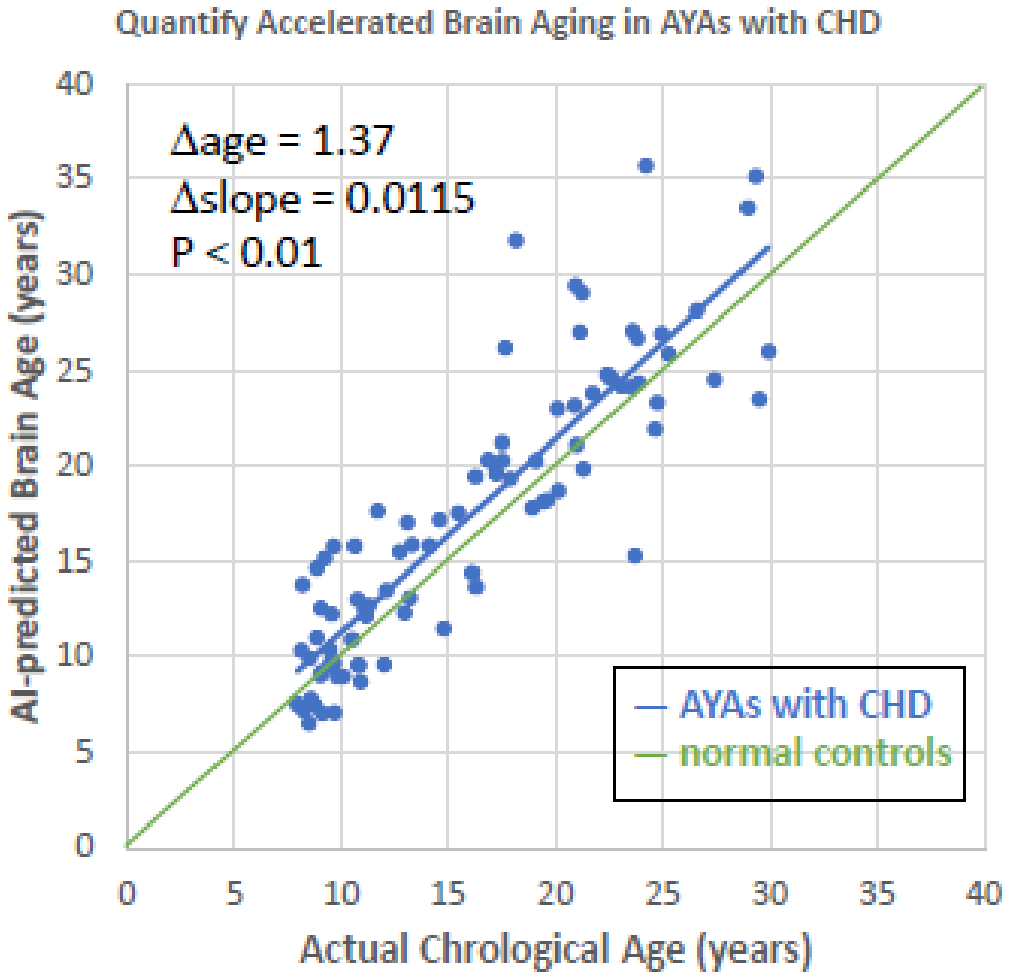
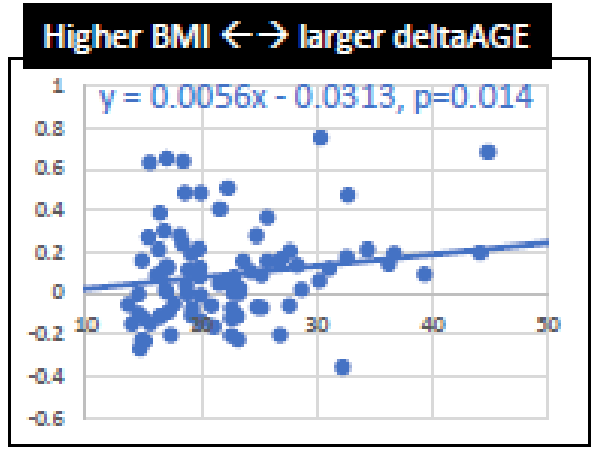
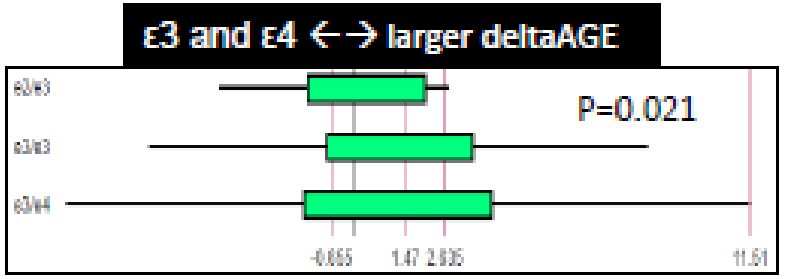
Non-lesional Biomarkers, Outcome Prediction



Contributing Factors

- Demographics
  - Sex
  - age at MRI
  - BMI
- Genetics
  - High brain expressed (HBE) gene, yes/no
  - Chromatin-modifying (CHR) gene, yes/no
  - Neurodevelopmental disorder (NDD) gene, yes/no
  - Constrained (PLI) gene, yes/no
  - ApoE (ε2/ε2, ε2/ε3, ε3/ε3, ε3/ε4, ε4/ε4)
- Socioeconomics status (SES)
  - Mother education
  - Father education
  - Family income





Lankalapalli et al, ASNR, 2022
Lankalapalli*, He*, et al, manuscript in prep. 2023

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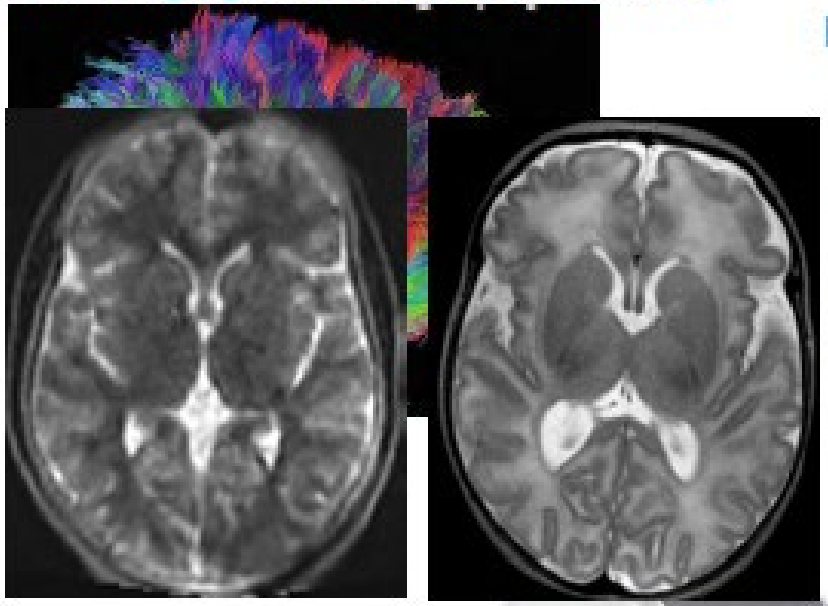
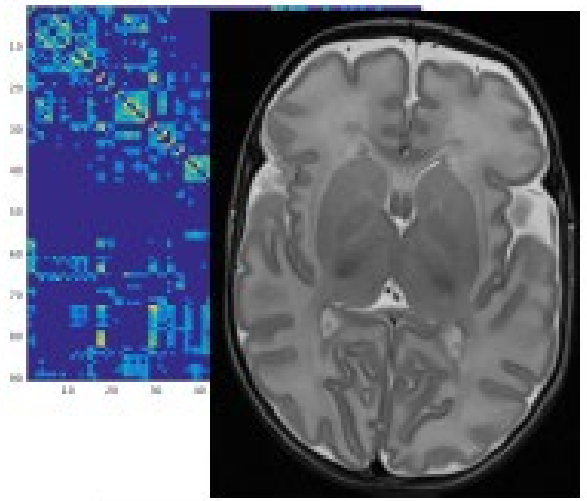
Modality and MR Scanner Choices

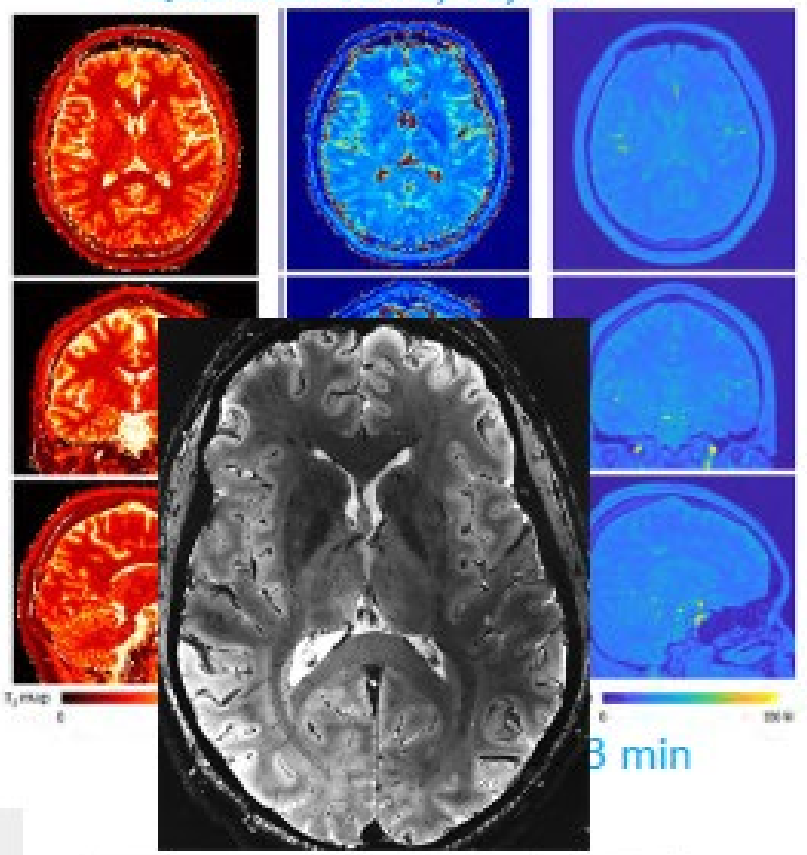
Diffusion Imaging / Structural Connectivity



Resting state fMRI
Functional Connectivity



Quantitative T1, T2, PD



3 min

0.064T

1.0T

NO structural or functional connectivity

3T

7T

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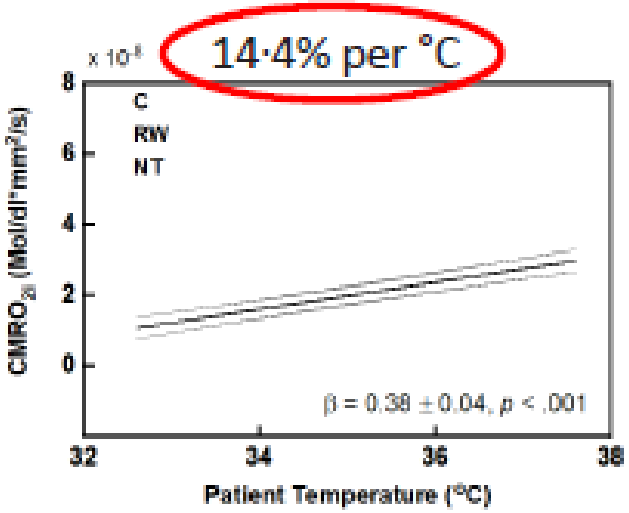
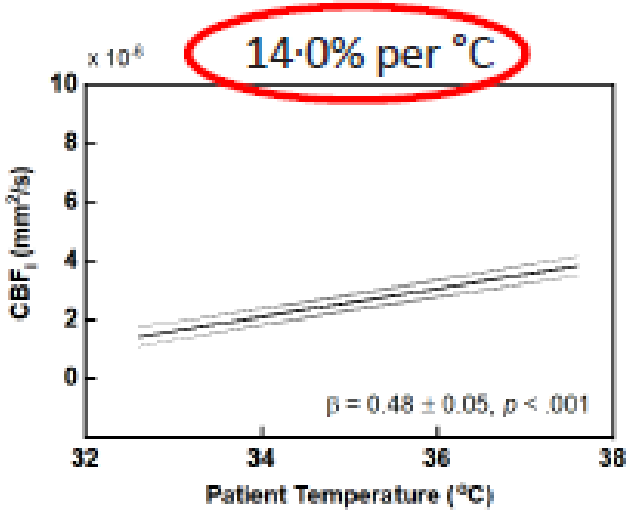
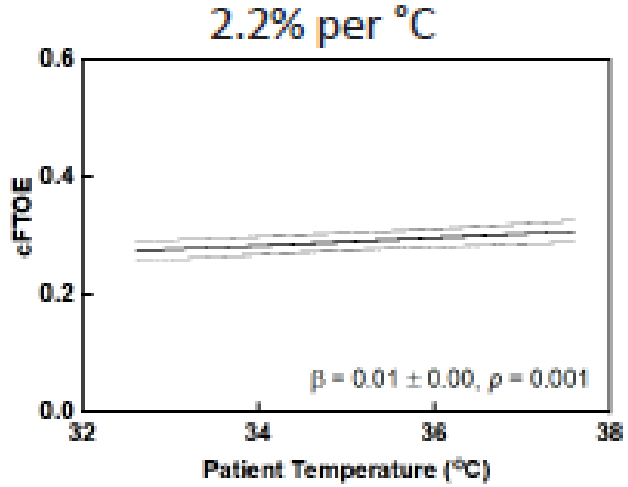
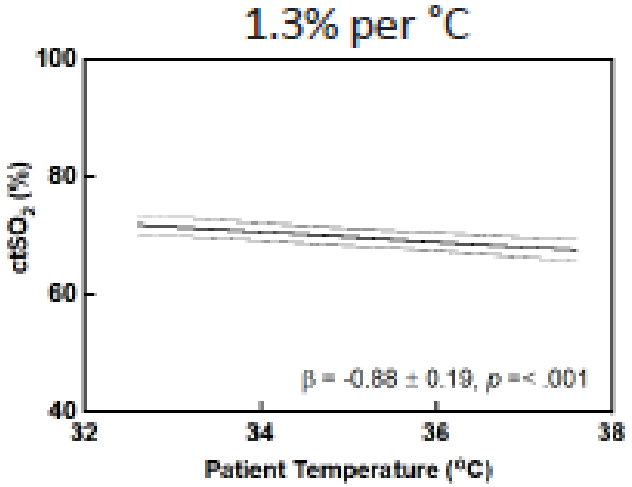
Bedside Biomarkers for Physiological Change, Outcome

Frequency Domain Near Infrared Spectroscopy
+ Diffuse Correlation Spectroscopy









- Cooling
- Rewarming
- Normothermia

Ivy Lin PhD

Jason Sutin PhD

N = 58 subjects cooled due to Dx of HIE
1 – 3 measurements per subject

R01HD076258 Grant, Soul, Lin

Sutin et al, eBiomedicine under revision

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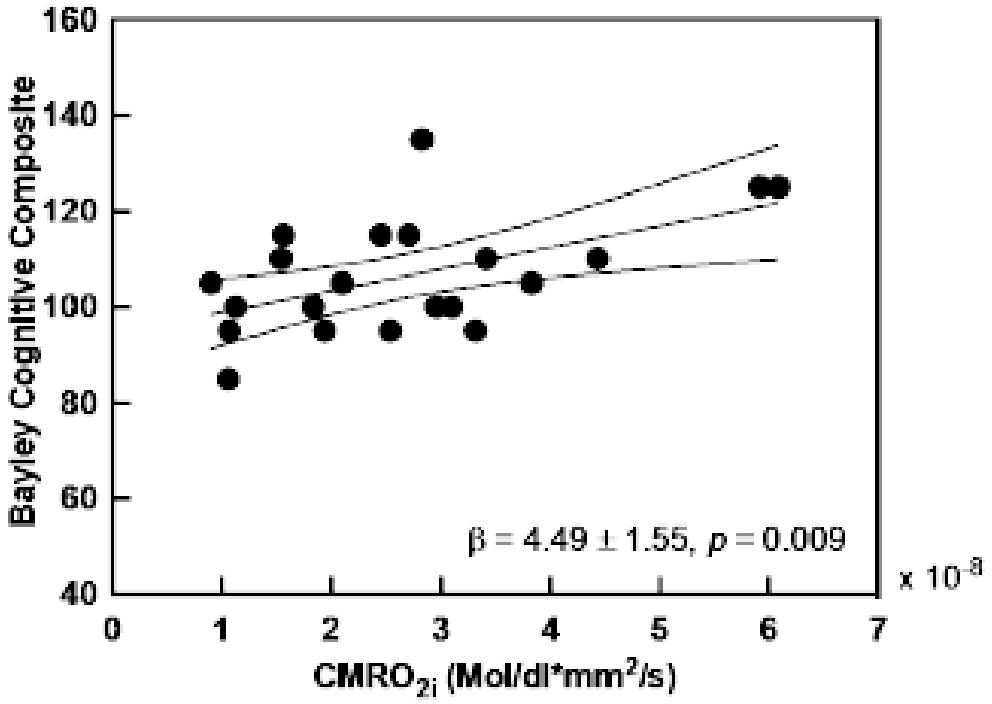
Bedside Biomarkers for Physiological Change, Outcome



Sutin et al, eBiomedicine under revision

- N=22 neonates with hypoxic ischemic encephalopathy
- Treated with therapeutic hypothermia
- *Frontal $CMRO_2$ after TH was only predictor of 18-month outcomes measured with BSIDIII*
- No correlation with MRI injury score (16/22 had normal MRIs)

R01HD076258 Grant, Soul, Lin

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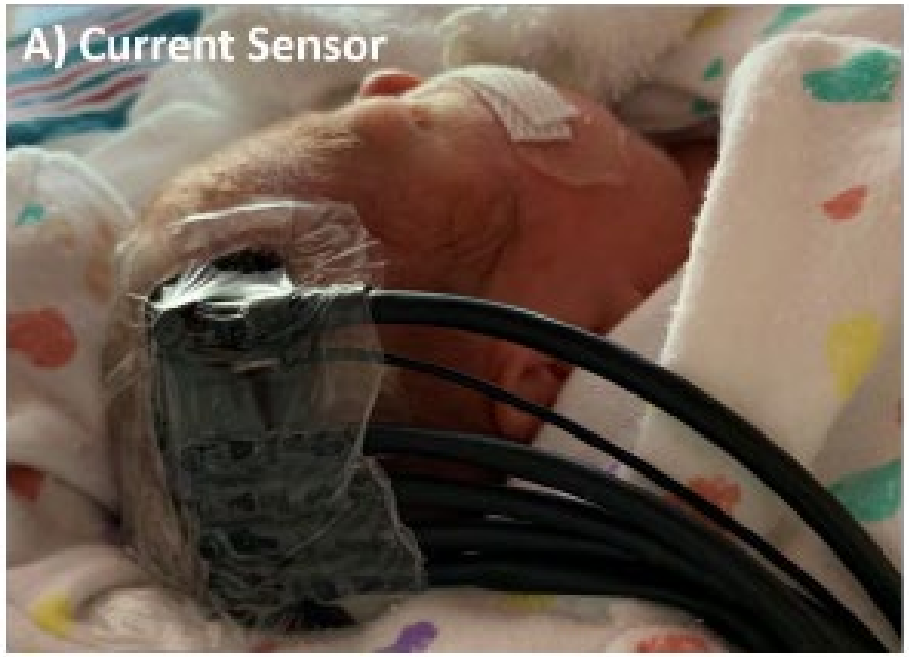

- Bedside high temporal resolution direct measure of cerebral oxygen consumption, CBF
- Develop physiological biomarkers for novel neonatal therapies aimed at neuroprotection
  - cerebrovascular resistance, autoregulation, critical closing pressure
- Framework for data driven explorations and future REAL TIME data analytics in the cloud

R01HD076258 Grant, Soul, Lin

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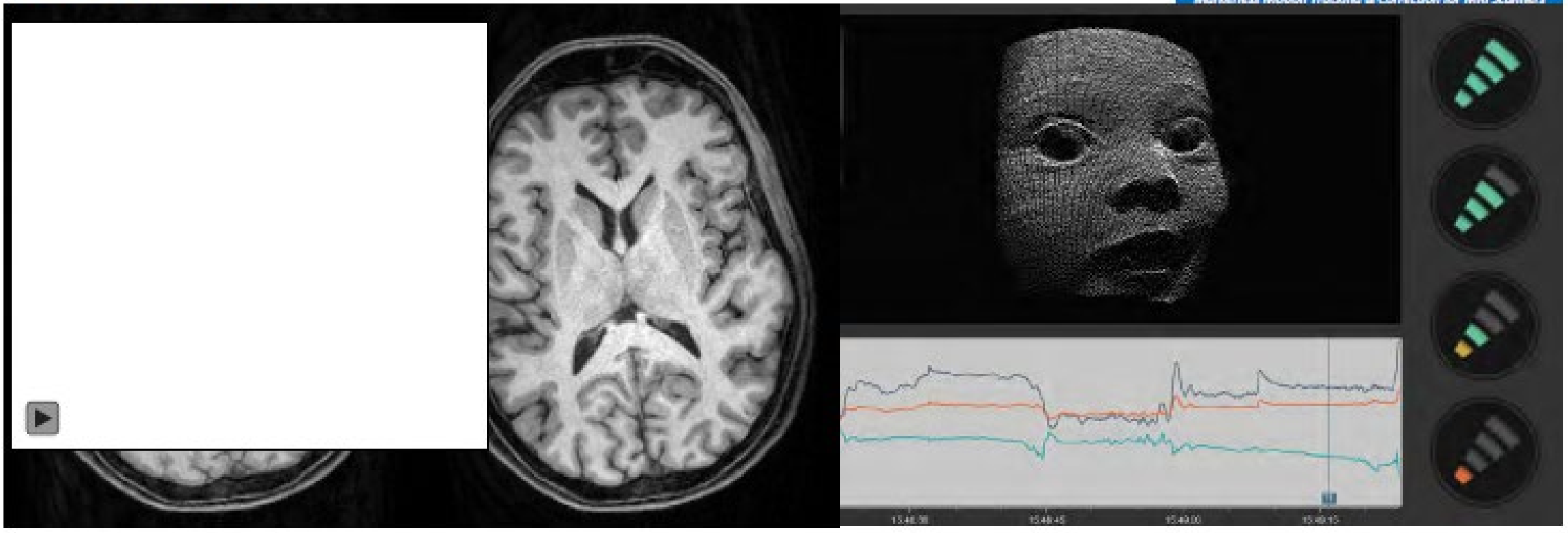
Motion

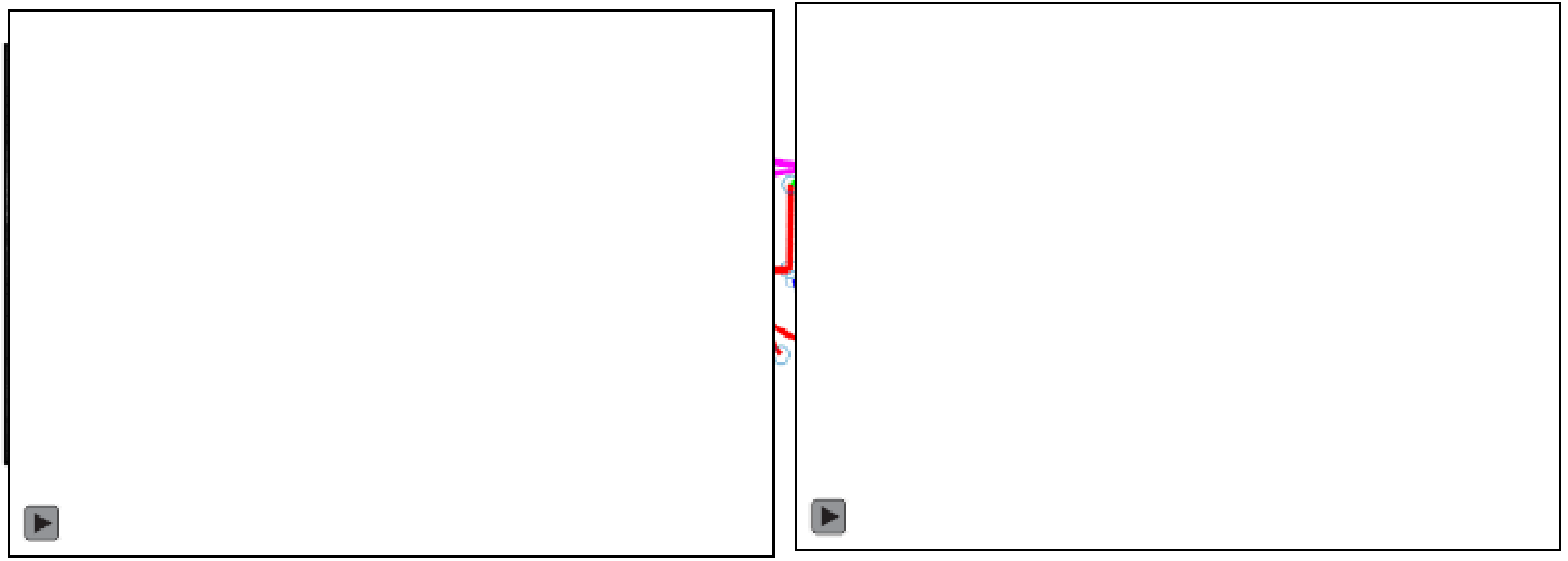


- Motion degrades image quality and can cause artificial differences
- Motion provides information on phenotype
- We need to discover ways to quantify and correct for motion

Frost et al. MRM 2019

Motion

A



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R01EB032708
R01HD100009

J Xu et al. MICCAI 2019; M Zhang et al 2020; J Xu et al. ISMRM 2021
Vasung et al. Developmental Neuroscience2022

Diversity Challenges

- Recruitment / Retention
  - Access to diverse communities can be limited even in routine clinical practice
  - Current databases limited representation or don't identify race, ethnicity
- Skin color
  - Dark skin colors are a challenge for quantitative optical imaging
- Motion
  - Infants of anxious mothers and with certain pathologies are less likely to fall asleep for an MRI or hold still for other studies
- Head shape and size
  - Limits quality of MRI and Magnetoencephalography

Pediatric Neuroimaging Biomarkers

- Challenging due to rapid changes in size, morphology and contrast as brain undergoes a critical period of self-organization
- Altered developmental trajectories may only become apparent years later, once the affected brain regions have become functional, therefore early biomarkers are essential
- Pediatric diseases are heterogenous collections of many different disorders without a dominant disease (ie no “Alzheimer's” for pediatrics)
- Need large data sets to combine multiple biomarkers – leverage prior studies across the lifespan, birth cohorts and clinical data
- Optimal modality for biomarker depends on time course, mechanism, magnitude of expected response in relation to development

Faculty


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R61NS126792
R01HD079484
OT2HL152640
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U01HD087211
R01HL135061
R01EB020613
R01EB024343
R01EB014947
R21HD058725

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