The Role of Brain Imaging in the NICU:

Lessons Learned & Future Directions in MRI Analysis

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Boston Children's Hospital
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Athinoula A. Martinos Center For Biomedical Imaging

HARVARD MEDICAL SCHOOL

MassGeneral for Children

Conflict of Interest Disclosure

We have no financial relationships with a commercial entity producing healthcare-related products and/or services

*photo consents have been obtained for all patient photos per MGH Partner's guidelines

MGH: Snapshot

- Patient care from conception through adulthood (1042 beds)
- Deliveries at MGH: 4000/year
- Deliveries in MGH Network: 12000/year
- MGH NICU admissions: 800/year
- Neonatal Transport Program – Boston MedFlight
- 24 hour in-house coverage by 12 Neonatologists
- Fetal Care Program
- NICU operating suites / ECMO
- Interdisciplinary, family-centered care
- Developmental Follow-up Clinic (network-wide)

- Magnet designation from the American Nurses Credentialing Center (ANCC)
  - *" Magnet achievement was a true team effort, made possible by the dedication, persistence and commitment of a wonderful team of nurses and others across the organization"*
- Largest hospital-based research enterprise in US (budget ~$930M)
- Ranks #1 in NIH funding (independent hospitals)
- Infant Brain Center (MGH Neuroscience)
- Perinatal Clinical Translational Research Committee

Come visit!

BRIGHAM AND WOMEN'S HOSPITAL

MassGeneral Hospital for Children

Harvard Neonatal-Perinatal Medicine Fellowship Training Program

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Beth Israel Deaconess Medical Center

Learning Objectives

- During patient case discussions, appreciate both the strengths and limitations of MRI

Focus: HIE

- Reflect upon the role of MRI in difficult diagnostic and therapeutic decisions
- Describe the technology and potential applications of machine learning algorithms in neonatal neuroimaging

Ex. HIE & NAS

Who Discovered MRI?

"The Shameful Wrong That Must Be Righted," New York Times, October 2003.

1950-1960's: Erwin Hahn – spin echoes

1968: First publication of NMR signals from a living animal

1970's: Major advancements: relaxation, diffusion, exchange of chemical water cells; different tissues. Raymond Damadian published in Science re: the differences detected between normal and abnormal (tumors) using NMR (Science, 1971)

1980's: MR angiography

1990's: fMRI, arterial spin labeling, FLAIR, DTI, SWI (WashU)

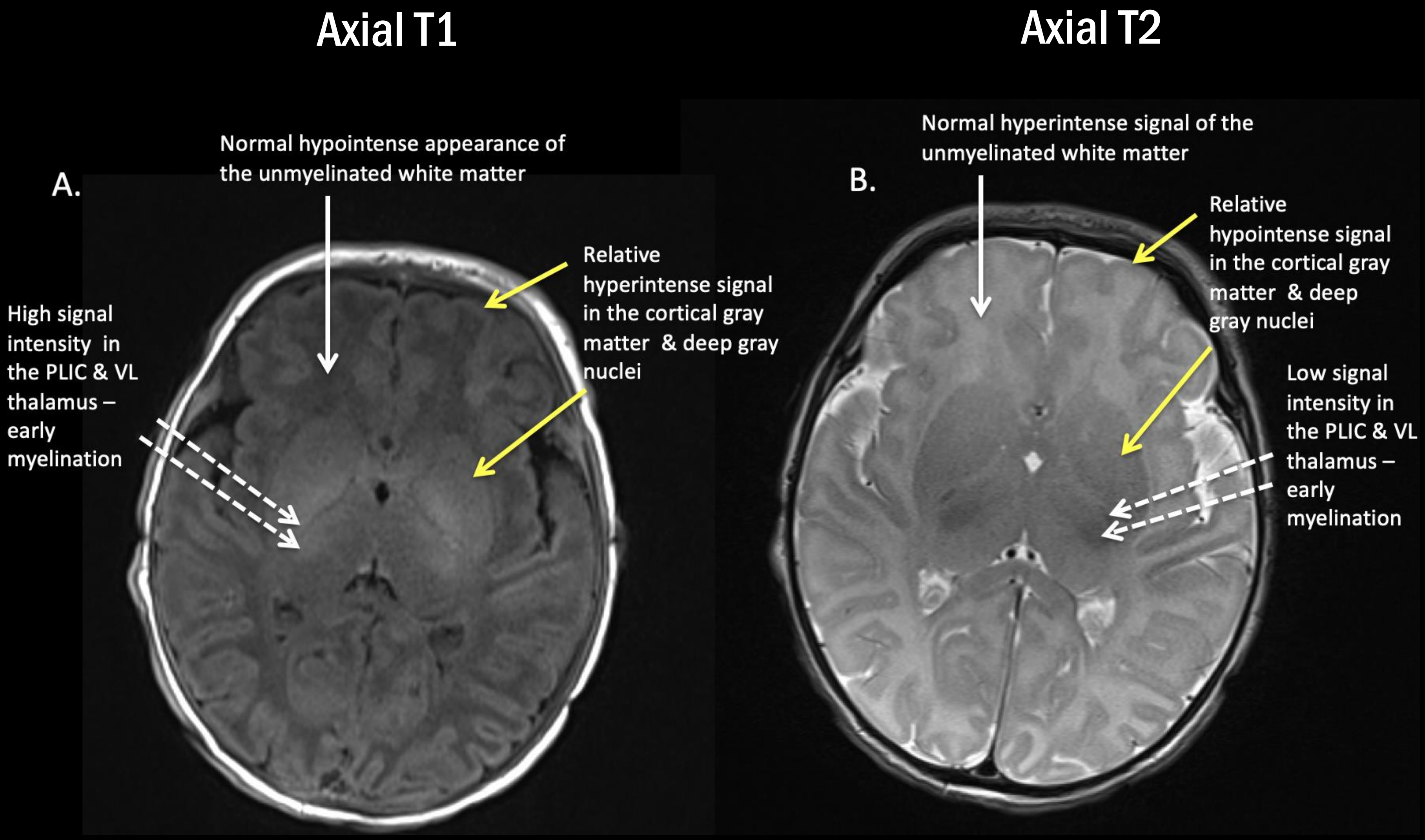
2000: Paul Lauterbur and Peter Mansfield - Nobel Prize (2003). Major technological advances re: Magnetoencephalography (MEG), Magnetic Resonance Spectroscopy (MRS), Optical imaging, Positron Emission Tomography (PET). <u>Continued advances in fetal and neonatal MRI.</u>

Damadian R. Tumor detection by nuclear magnetic resonance. Science 1971; 171:1151-3.

Neonatal MRI

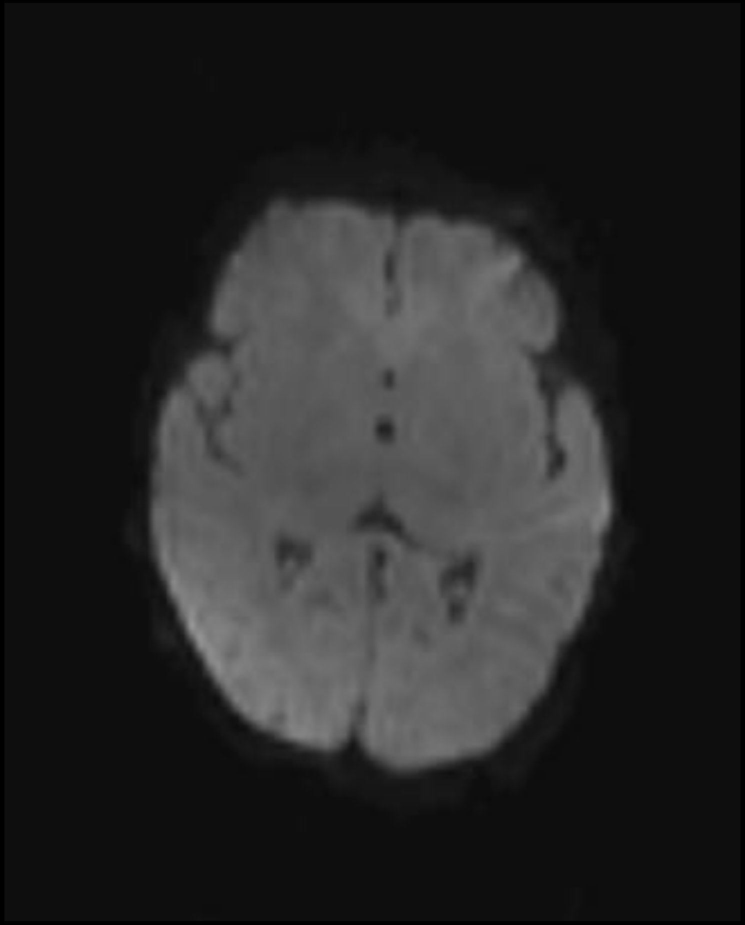
- Most sensitive, noninvasive imaging modality for the documentation of neonatal brain injury
- Challenges: injuries may be over or under called
  - Rapidity of myelination and microstructure maturation of white matter, gyrification, volume, cortical thickness, differences in regional development etc
  - Many technical challenges too
- Uncommon disorders may be misdiagnosed as HIE

Normal MRI: 3 day-old FT Infant

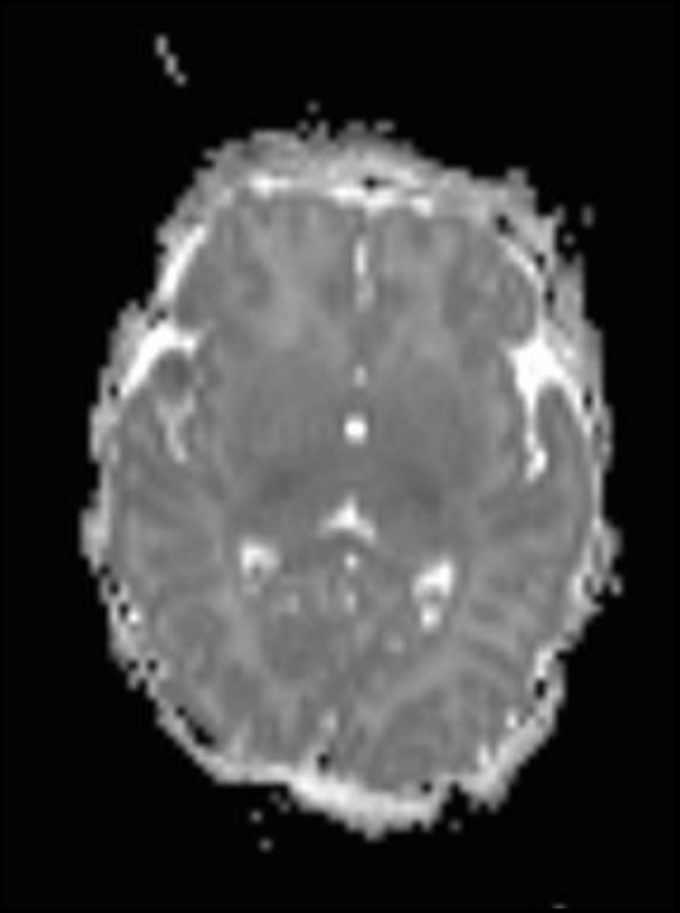


Normal MRI: 3 day-old FT Infant

DWI



ADC: Calculated from DWI



ADC: low SI in PLIC and VL thalamus: NORMAL. Water can't move as freely between myelin sheaths (physiologic)

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Clinical Case Examples

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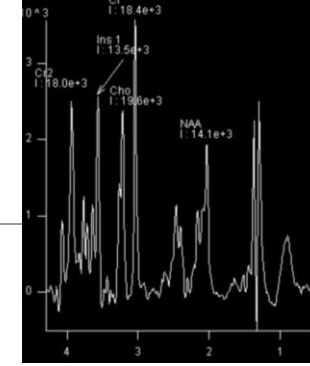
Case 1: Clinical Presentation

- 40 6/7 week male infant (3680 grams; 44th%) born via vaginal delivery to a 22 yo G1PO mother
- Maternal hx notable for GBS+, obesity, anxiety and depression (not on meds
- Cat II fetal tracing; chorio, meconium
- Infant was non-vigorous; PPV, ETT (passive cooling commenced)
- Apgars 1, 3, 5
- UCB: (a) pH 7.0, BD 14.5

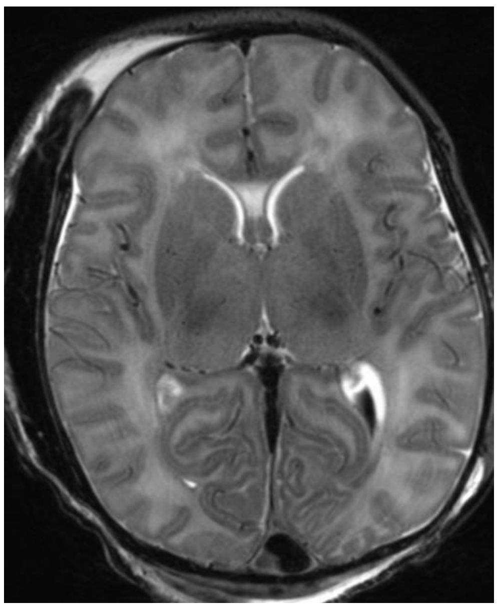
Case 1: Clinical Presentation

- Initial neuro exam: no spontaneous movement, hypotonic, absent grasp, no suck
- Full montage EEG (Diffuse voltage attenuation)
- Early MRI obtained prior to rewarming
- When do you typically perform MRI?
    - <7 days
    - >7 days
    - both
    - other

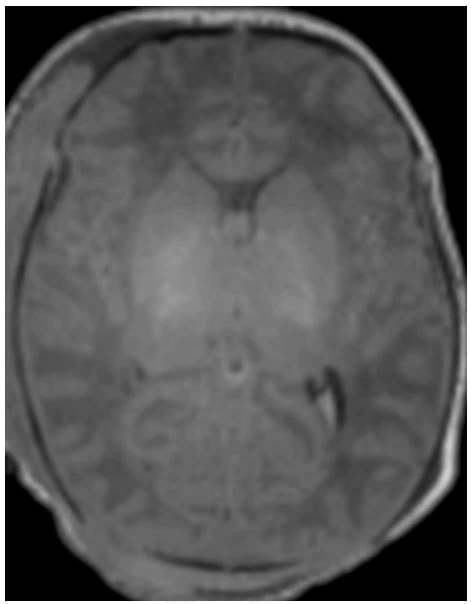
Case 1: Imaging



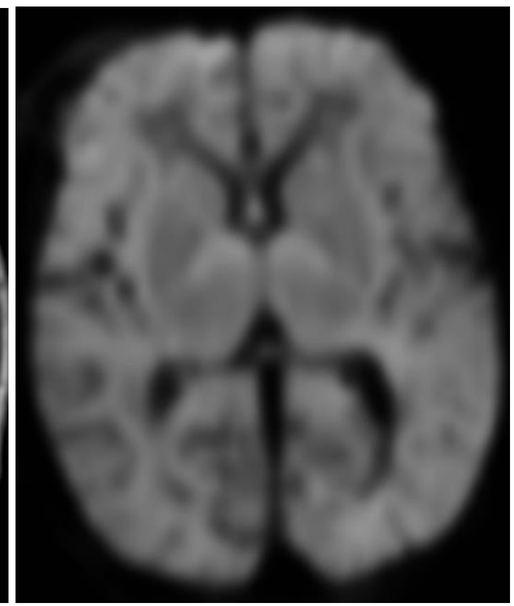
T2



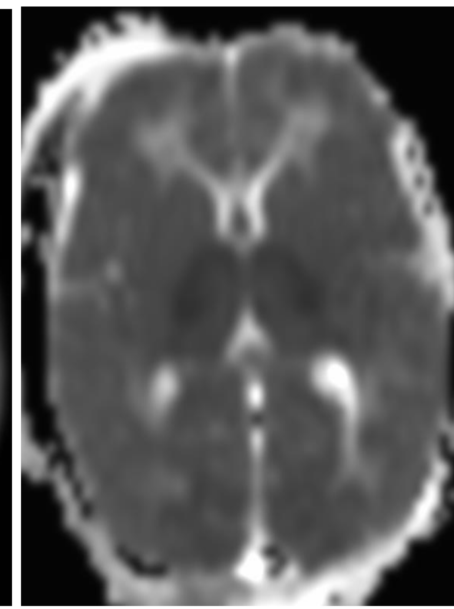
T1



DWI



ADC



Imaging compliments of P. Ellen Grant, MD

Case 1: Clinical Course

- Diagnosis: Severe HIE
- Family wished to re-direct care to comfort measures
- Infant passed peacefully in mother's arms
- Placenta 40th% - multiple infarctions
- Post mortem
  - Neuropath: extensive hypereosinophilic change in neurons throughout the brain and marked astrogliosis throughout the white matter consistent with perinatal HII
  - No infection or hemorrhage

Case 1: Take home points

- Limitations of fetal monitoring
- Maintain a broad differential for encephalopathy
- Contributions of placental and post-mortem pathology

Case 3: Clinical Presentation

- 39 2/7 week male (BW 3700 grams) born via stat cesarean section due to decreased fetal movement
- Born to a 39 yo G2P1 mother with negative prenatal screens. History notable for T1DM (insulin dependent)
- Apgars 1, 6, 7
- Required several minutes of PPV
- Umbilical arterial gas 6.8, BD 17
- Passive cooling started
- Infant transferred to level III NICU

Case 2: Clinical Course

- Required CMV and iNo for PPHN
- Completed 72 hours of TH
- EEG without seizures and normal background s/p cooling
- Prolonged hospitalization
- Normal MRI

Case 2: Take home points

- A negative MRI is encouraging
  - ~ 50% will have good outcomes
  - ~ 30% will have mild outcomes
  - ~ 20% will have moderate- severe outcomes[1]
- EEG adds additional useful information
- Don’t forget about channelopathies (e.g. KCNQ2) when HIE, metabolic, infection ruled out

Shankararan et al J of Pediatrics.2015

Case 3: Clinical presentation

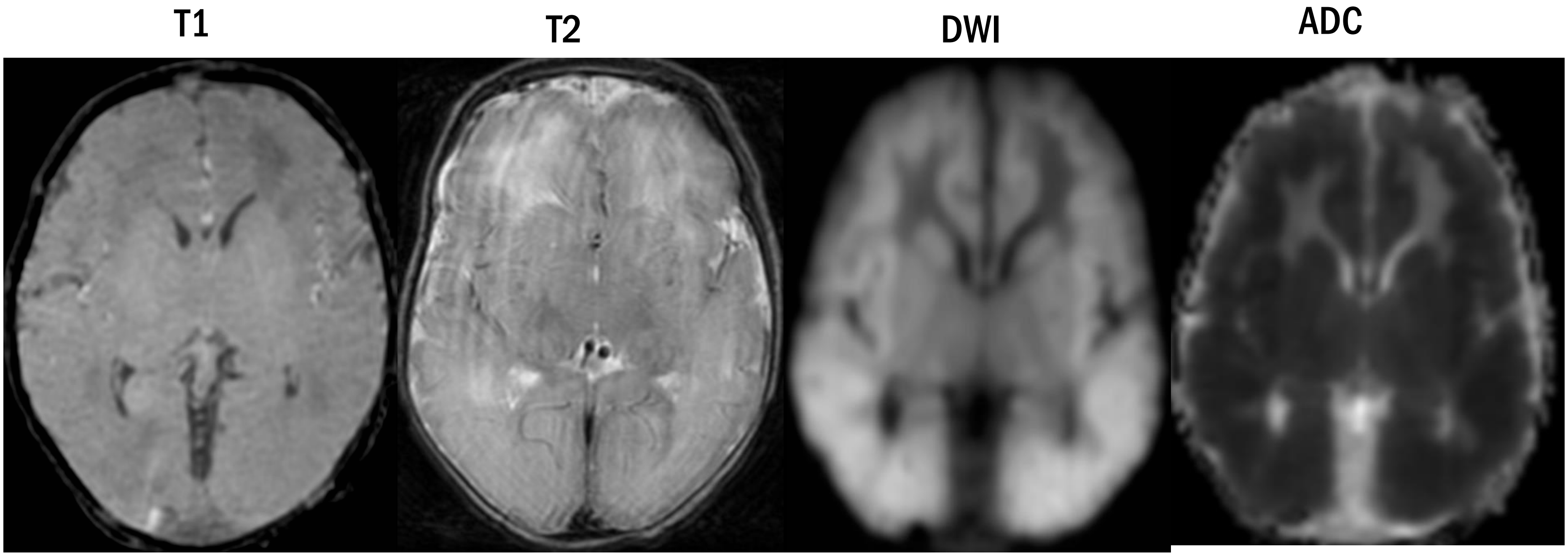
Pre- cooling era

- 40 4/7 week male infant born via stat c-section d/t NRFHT
- 21 yo mother – no significant history; prenatal labs unremarkable
- 30 seconds of PPV; APGAR scores 5, 9
- BW 4065 grams (95^{th}%), L 54.5 cm (95^{th}%), HC 37 cm (95^{th}%)
- DOL1 he was noted to be lethargic and hypotonic
- Septic work-up initiated and transferred to the NICU
- DOL3 developed apnea and seizures

Case 3: Clinical course

- Intubated
- Phenobarbital, Dilantin
- LTM
- LP, HSV PCR, gas, BMP, lactate, pyruvate, urine organic acids, serum amino acids
- Followed by pediatric neurology and metabolism

Case 3: Imaging



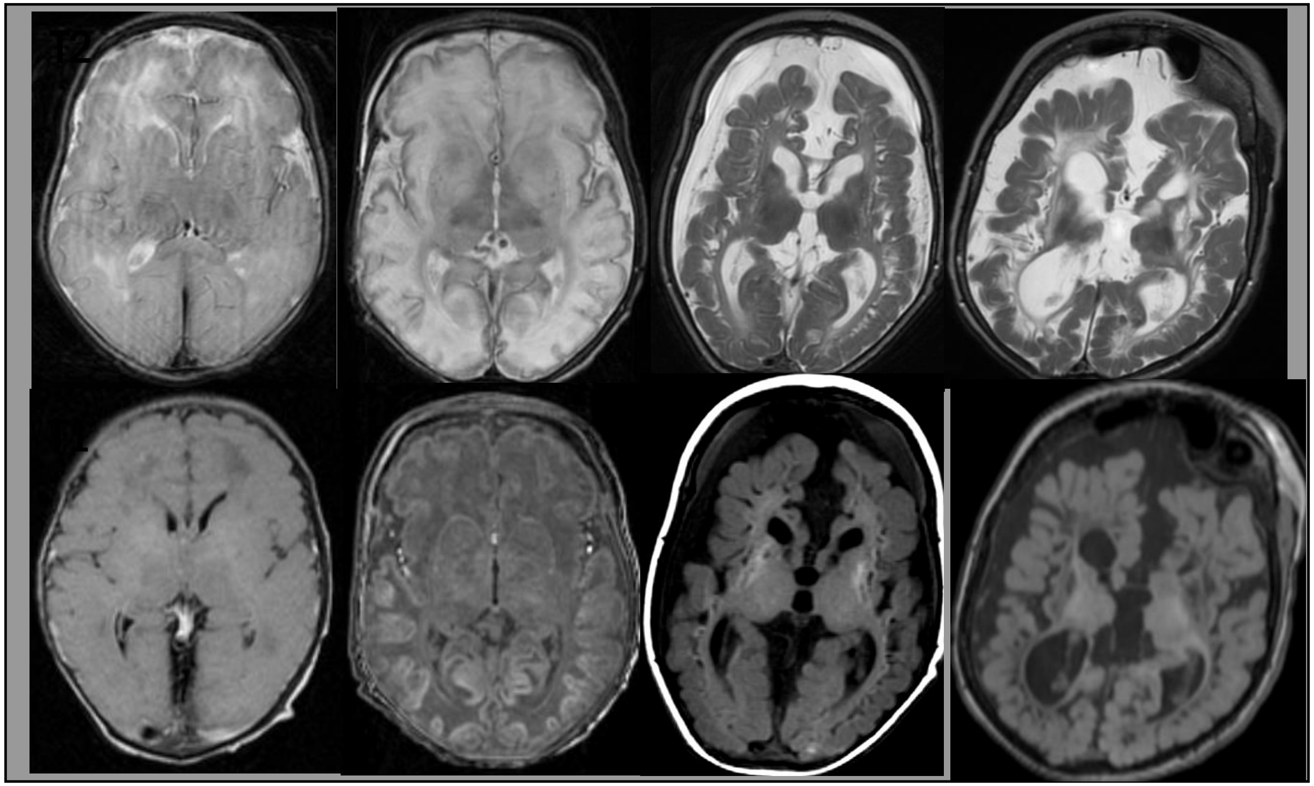
Imaging compliments of P. Ellen Grant, MD

Case 3: Clinical course

- Metabolism
  - Urinary sulfites present on dipstick
  - Elevation of urinary thiosulfate and s-sulfocysteine
  - Normal serum uric acid
- Diagnosis: Sulfite Oxidase Deficiency (SOD)
- X-Met, X-Cys Analog formula
- Discharged with g-tube and AEDs
- 4 month follow-up notable for: lack of visual tracking, hypertonia, myoclonic jerks, exaggerated moro reflex, bilateral up-going toes

Sulfite oxidase deficiency

Evolution



4 Days 10 Days 3 mo 3yrs

Imaging compliments of P. Ellen Grant, MD

Case 3: Take home points

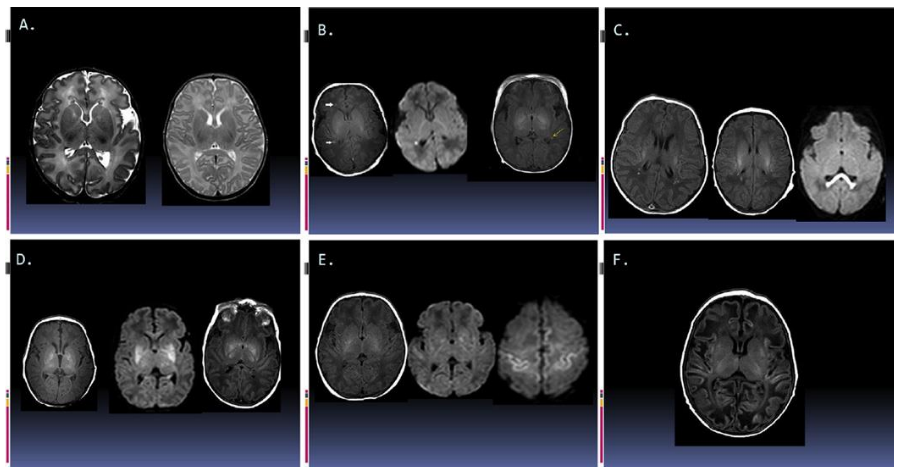
- Neurometabolic disorders – may have features similar to HIE
- Never presume an infant with encephalopathy has HIE
  - Implications for: infant care, family, OBGYN
- Delayed onset of encephalopathy consider other etiologies (metabolic, infection, stroke)
- Timing matters

Isolated SOD:
Lips
Philtrum
Microcephaly
Seizures
Cognitive delays

GeneReviews

HIE MRI Interpretation

- Current clinical practices for analyzing the ADC maps is a visual assessment
- Scoring systems –Shankaran S, McDonald SA, Laptook AR, Hintz SR, Barnes PD, Das A, Pappas A, Higgins RD



Scoring systems:

- Barkovich (1998)

- Rutherford (2010)

- De Vries (2018)

A, NICHD NRN score = 0 (Term infants; normal T2(3T and 1.5T)). **B**, NICHD NRN score 1A with minimal cerebral lesions only without any involvement of the basal ganglia, thalamus, ALIC, PLIC, or WS infarction. **C**, NICHD NRN score 1B with more extensive cerebral lesion without any BGT, ALIC, PLIC, or infarction. **D**, NICHD NRN score 2A: any BGT, ALIC, PLIC, or WS infarction without any other cerebral lesions. **E**, NICHD NRN score 2B: BGT, ALIC, PLIC, or WS infarction and cerebral lesions. **F**, NICHD NRN score 3: cerebral hemispheric devastation.

Shankaran S, McDonald SA, Laptook AR, et al. Neonatal Magnetic Resonance Imaging Pattern of Brain Injury as a Biomarker of Childhood Outcomes following a Trial of Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy. *J Pediatr*. 2015;167(5):987–93.e3. doi:10.1016/j.jpeds.2015.08.013

MRI Interpretation

- Limitations, challenges, & pitfalls
- 20-50% uncertainty/errors in radiologists' interpretation of ADC maps in neonates with HIE[1-2]
- What are the normal regional ranges of ADC variation?
- How low is too low? What about high values?
- Need for: quantifiable, precise, reproducible measurements

1. Goergen SK, Ang H, Wong F, et al. Early MRI in term infants with perinatal hypoxic–ischemic brain injury: Interobserver agreement and MRI predictors of outcome at 2 years. *Clinical radiology*. 2014;69(1):72-81.
2. Ozturk A, Sasson AD, Farrell JAD, et al. Regional differences in diffusion tensor imaging measurements: assessment of intrarater and interrater variability. *American Journal of Neuroradiology*. 2008;29(6):1124-1127.

Improving neonatal MRI interpretation & the role of imaging informatics

Utilization of legacy health care data

Research Patient Data Registry (RPDR)

- Shawn N Murphy
- Christopher Herrick
- Mariah Mitchell
- Stacey Duey
- Laurie Bogosian
- Eugene Braunwald
- Anne Klibanski
- Henry Chueh

Medical Imaging Informatics Bench to Bedside Mi2b2

- Randy Gollub
- Christopher Herrick
- Bill Wang
- David Wang
- Kathy Andriole
- Darren Sack
- P Ellen Grant
- Nathaniel Reynolds
- Kallirroi Retzepi
- Rudolph Pienaar
- Victor Castro
- Steve Pieper
- Lilla Zollei
- Yangming Ou

Mi2b2 engine: https://www.nmr.mgh.harvard.edu/lab/mi2b2
[Murphy et al, 2015]

NIH RO1 EB014947
NIH R01 AT006364
NIH R01 AT005280
NIH P01 AT006663

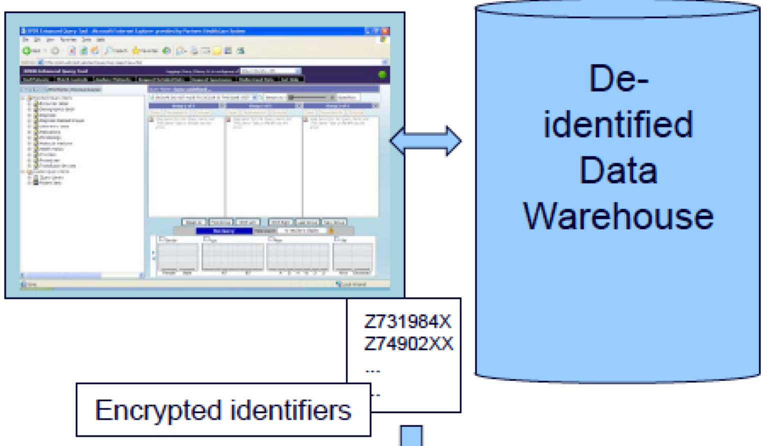
Efficiently reaching a larger N with lower cost

Research Patient Data Registry (RPDR) at Partners Healthcare to find patient cohorts for clinical research

1) Queries for aggregate patient numbers

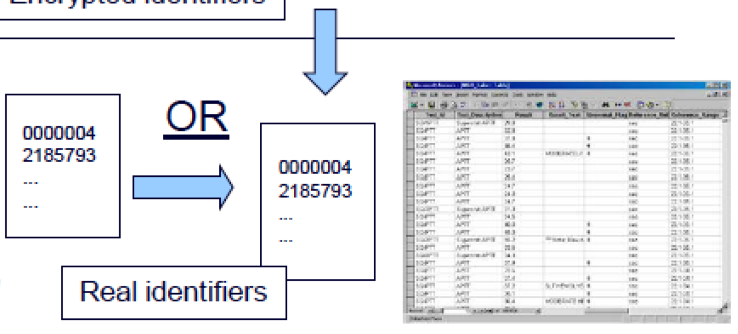
- Warehouse of in & outpatient clinical data
- 6.5 million Partners Healthcare patients
- 2.2 billion diagnoses, medications, procedures, laboratories, & physical findings coupled to demographic & visit data
- Authorized use by faculty status
- Clinicians can construct complex queries
- Queries cannot identify individuals, internally can produce identifiers for (2)

Query construction in web tool

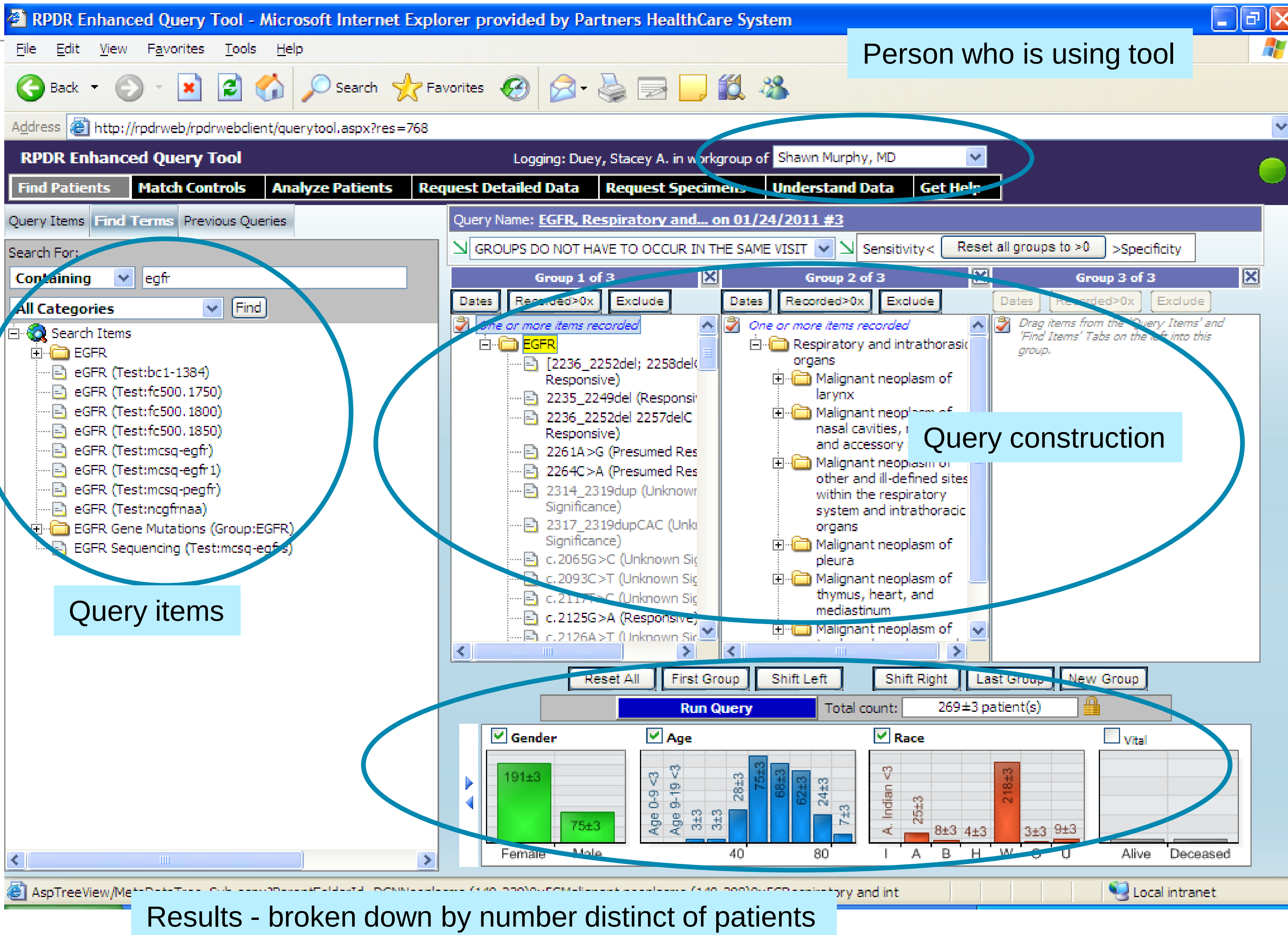


2) Returns detailed patient data

- Start with list of specific patients, usually from (1)
- Authorized use by IRB Protocol
- Returns contact and PCP information, demographics, providers, visits, diagnoses, medications, procedures, laboratories, microbiology, reports (discharge, LMR, operative, radiology, pathology, cardiology, pulmonary, endoscopy), and images into a Microsoft Access database and text files.



Finding Patients with RPDR



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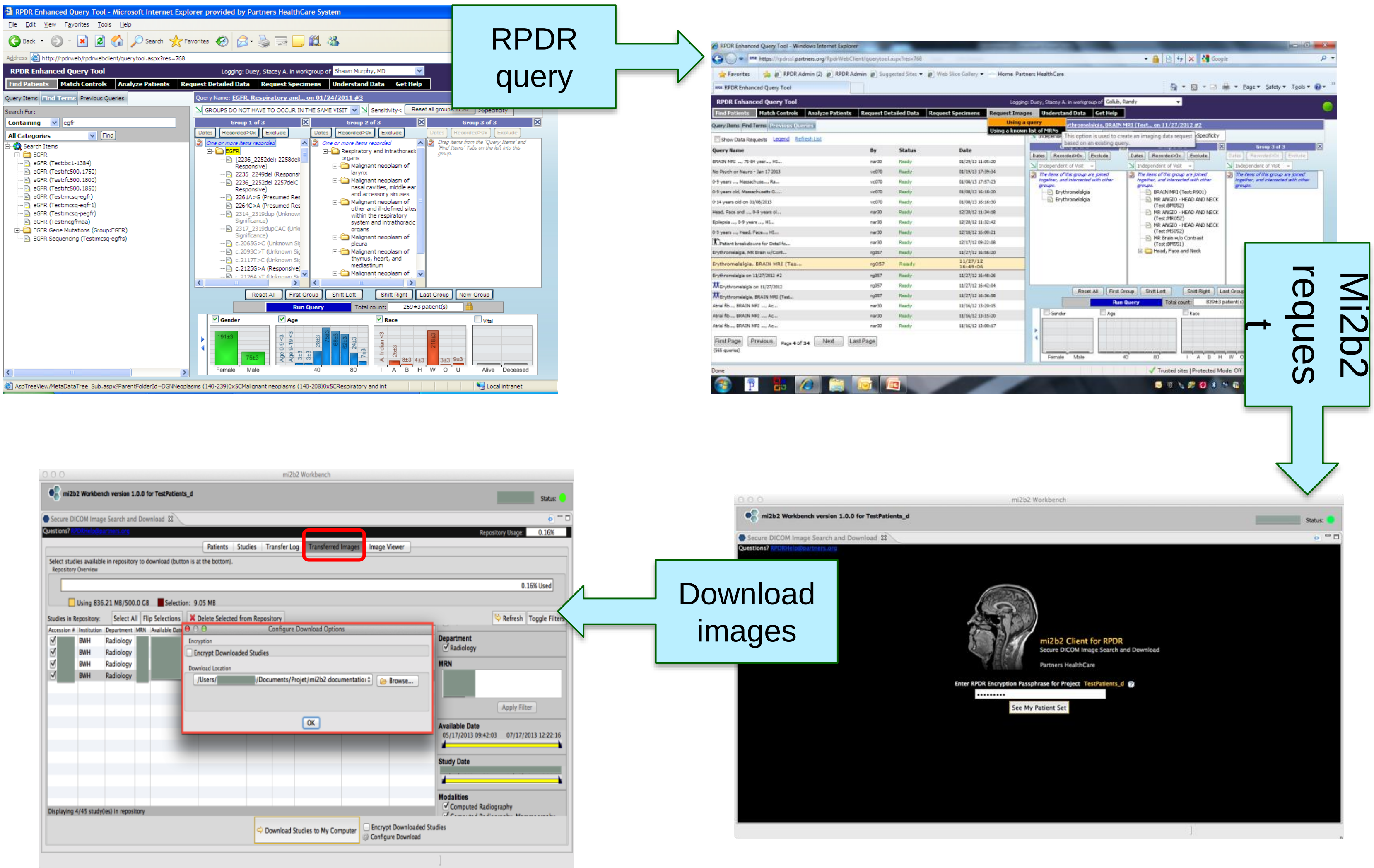
Find “normative cases” ages 0-6 yrs



RPDR & mi2b2 Pipeline: Data Extraction Example

Accessible to & may benefit:

- Data scientists
- Data base engineers
- Medical image analysis algorithm developers
- Machine learning experts (mine in a meaningful way)
- Clinician scientists
- Image acquisition experts
- Radiology Decision Support developers
- Clinical care teams

Mi2b2 engine: https://www.nmr.mgh.harvard.edu/lab/mi2b2
[Murphy et al, 2015]

The Start of an Atlas: Finding Normative Data

- How do we know what is “normal?”
- How do we obtain images?
- Research Patient Data Registry (RPDR) used to query EHR → Medical Imaging Informatics Bench to Bedside (mi2b2) software → access identified pts from PACS at MGH

N = ~100,000
- Brain MRI (MGH)

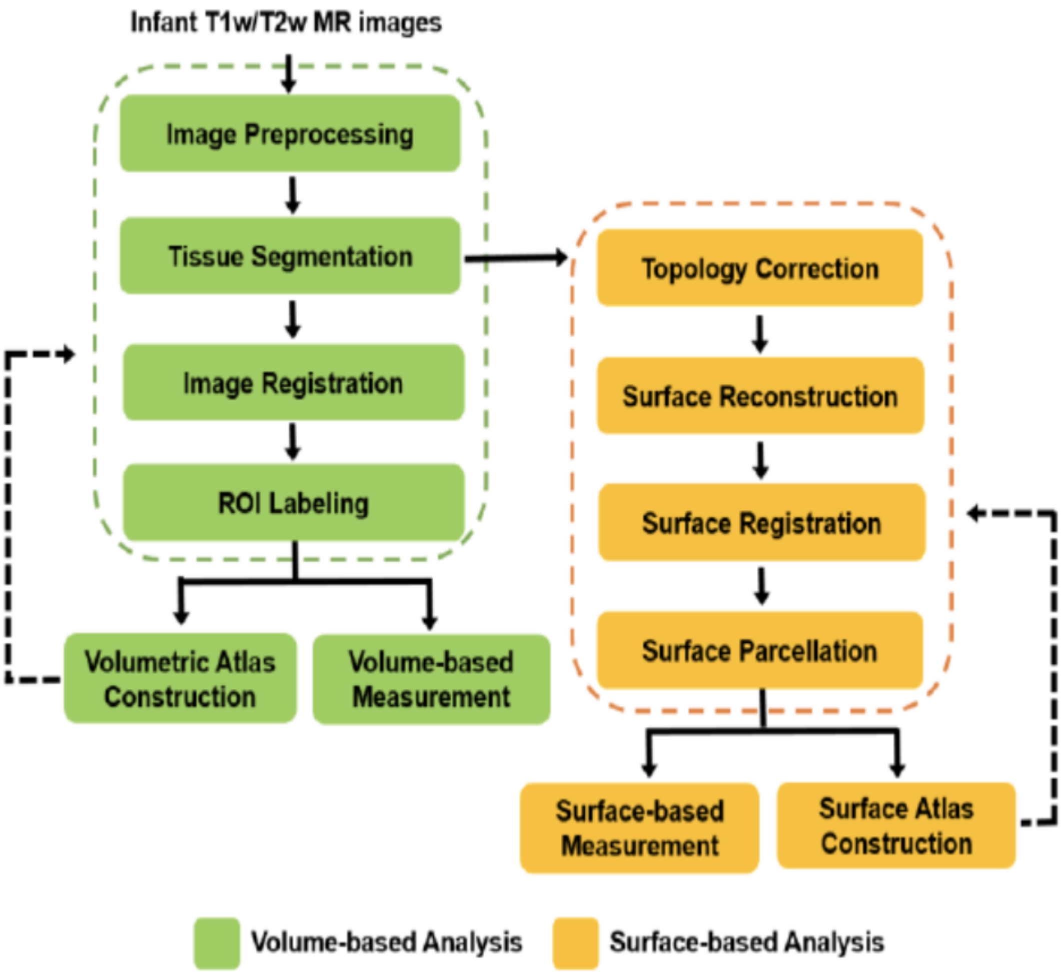
N = 2,871
- **Scanned 2006-2013 with ADC maps in Siemens 3T scanner**
- **0-6 years old at the time of scan**
- **Radiological reports suggesting free of abnormality**

N = 1,648
- ADC maps found and not corrupted

N = 705
- ADC maps re-examined & confirmed to be normal by expert clinicians

N = 201
- Duplicates removed
- Still normal 3 years after the initial visit

Basic pipeline for analyzing structural images



Neuroimage. 2019 Jan 15;185:906-925. doi: 10.1016/j.neuroimage.2018.03.042. Epub 2018 Mar 21. Computational neuroanatomy of baby brains: A review.

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Image analysis

*website references provided at the end

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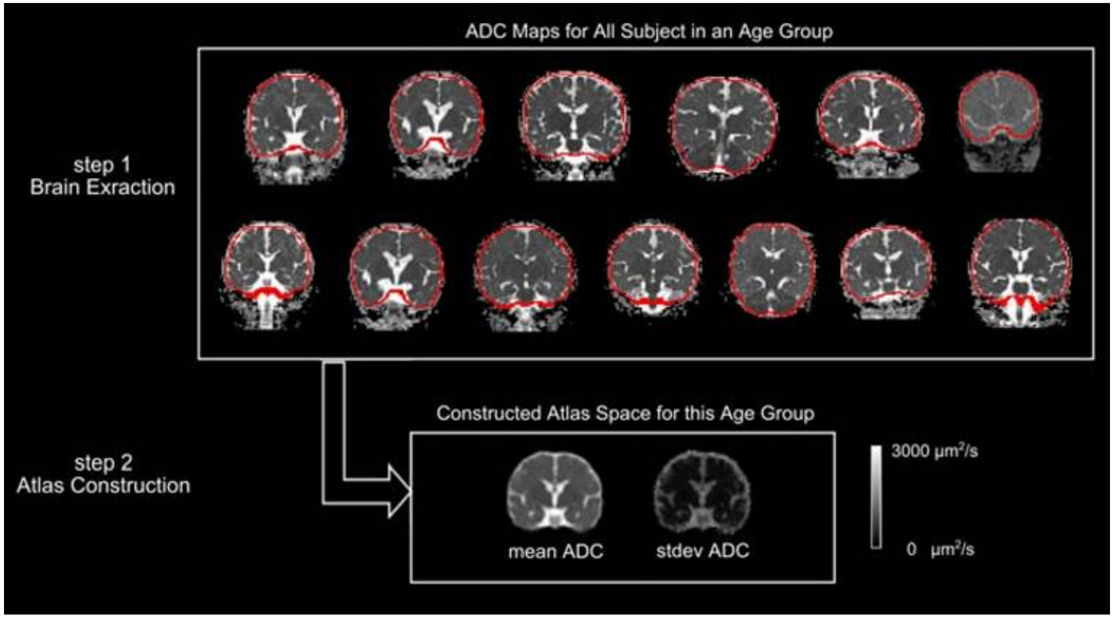
- 1. Field of View Normalization
- 2. Skull Stripping
- 3. Automatic Structural Segmentation
- 4. Multi-modal/channel Fusion
- 5. Tissue Density and Morphometry
- 6. Atlas Construction
- 7. Lesion Detection
- 8. Longitudinal Change Quantification
- 9. Machine learning to predict clinical variables

Based on DRAMMS Registration (2, 3, 4, 5D) [Ou'11, '12, '14a,b, '15]
Based on BEFI Machine Learning [Ou'09, '17 (u.r.)]

Data Analysis – Atlas Construction

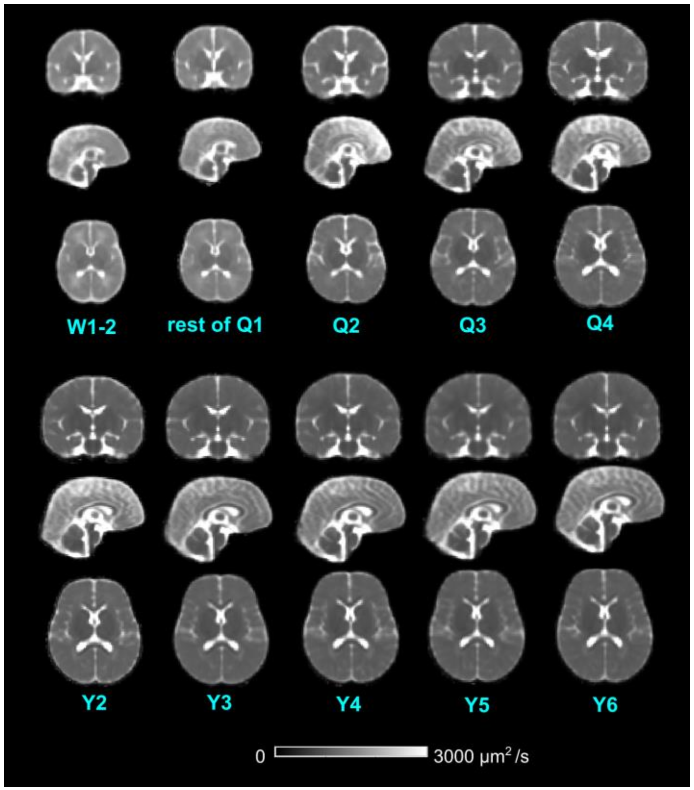
Age	Y1					Y2	Y3	Y4	Y5	Y6	**Total**
	W1-2	Rest of Q1	Q2	Q3	Q4						
# Subjects	13	13	8	8	13	34	33	25	21	33	**201**
# Females	4	5	4	5	5	17	14	14	10	15	**93**



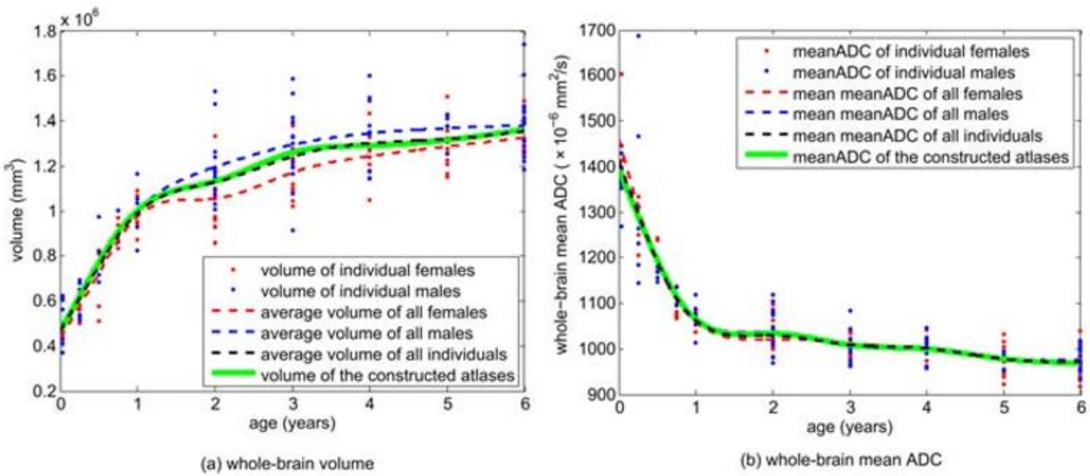
* Ou et al, MedIA, 2011 (Most Cited Articles)
* Ou et al, IEEE TMI (Most Popular Articles)
* Ou et al, OHBM, 2014, 2015, 2017
* Ou et al, NeuroImage, 2015
* Ou et al, HBM, 2017

[Software for Atlas Construction]
https://www.nitrc.org/projects/popdramms
[Atlases released]
https://www.nitrc.org/projects/mgh_adcatlases

Validation – are the atlases right?



Whole-brain volume and ADC values, and changes

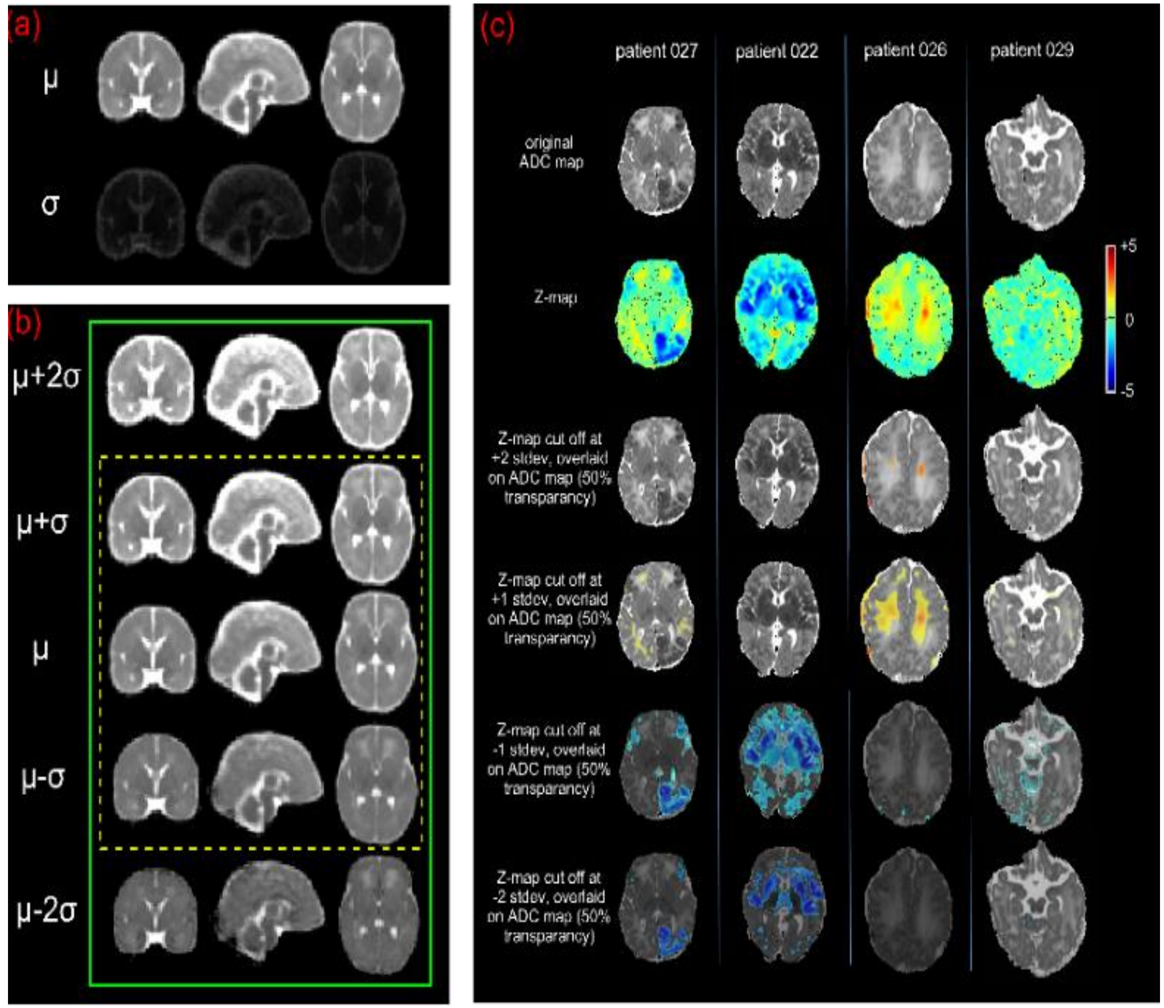


[Software for Atlas Construction] https://www.nitrc.org/projects/popdramms
[Atlases released] https://www.nitrc.org/projects/mgh_adcatlases

Detecting Outliers

Abnormality detected as outliers to the characterized normal ranges of ADC values

Quantitative comparison of patient's ADC values to the population mean and stdev, at the voxel level



Ou Y, Zöllei L, Retzepi K, Castro V, Bates SV, Pieper S, Andriole KP, Murphy SN, Gollub RL, Grant PE. Using clinically acquired MRI to construct age-specific ADC atlases: Quantifying spatiotemporal ADC changes from birth to 6-year old. ***Hum Brain Mapp*. 2017** Jun;38(6):3052-3068. doi: 10.1002/hbm.23573. Epub 2017 Mar 31. PubMed PMID: 28371107; PubMed Central PMCID: PMC5426959.

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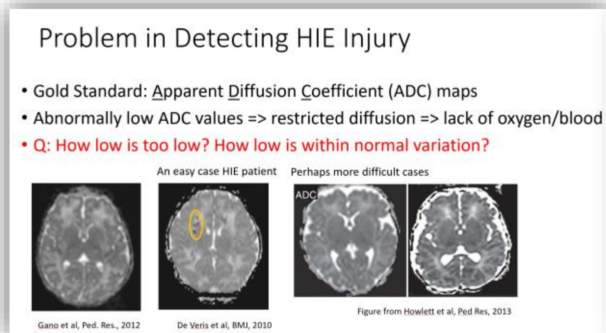
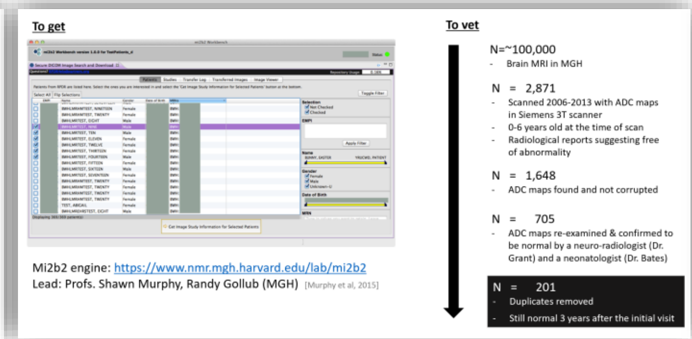
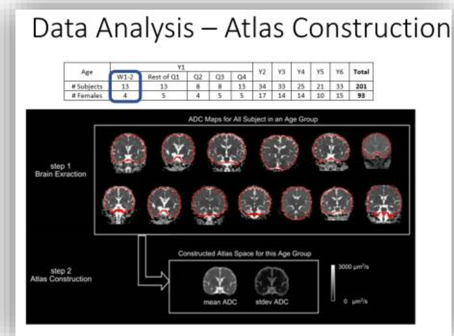
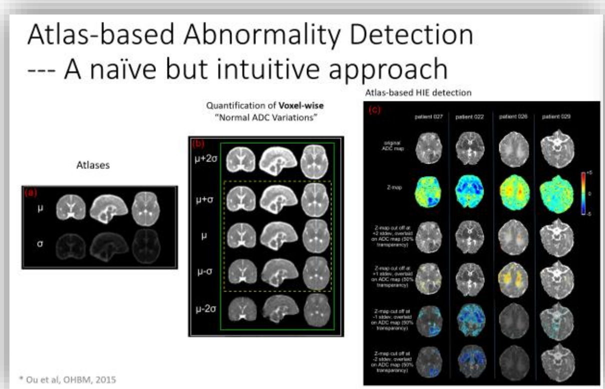
How to detect HIE lesions automatically and accurately?

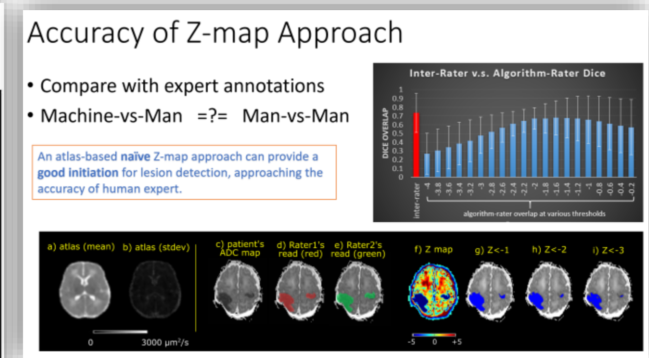
- Done: created normative ADC atlases for abnormality detection











[Publications]
* Ou et al, MedIA, 2011 (Most Cited Articles)
* Ou et al, IEEE TMI, 2014 (Most Popular Articles)
* Ou et al, OHBM, 2014, 2015, 2017
* Ou et al, NeuroImage, 2015
* Ou et al, HBM, 2017
* Ou et al, Neuroinformatics, 2018

[Software for Atlas Construction]
* Ou et al, https://www.nitrc.org/projects/popdramms

[Atlases released]
* Ou et al, https://www.nitrc.org/projects/mgh_adcatlases

Machine Learning:

- Computer aided patterns/maps
- Learned models & the application to medical images
- Algorithm development:
  - Lesion detection
  - Outcome prediction

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

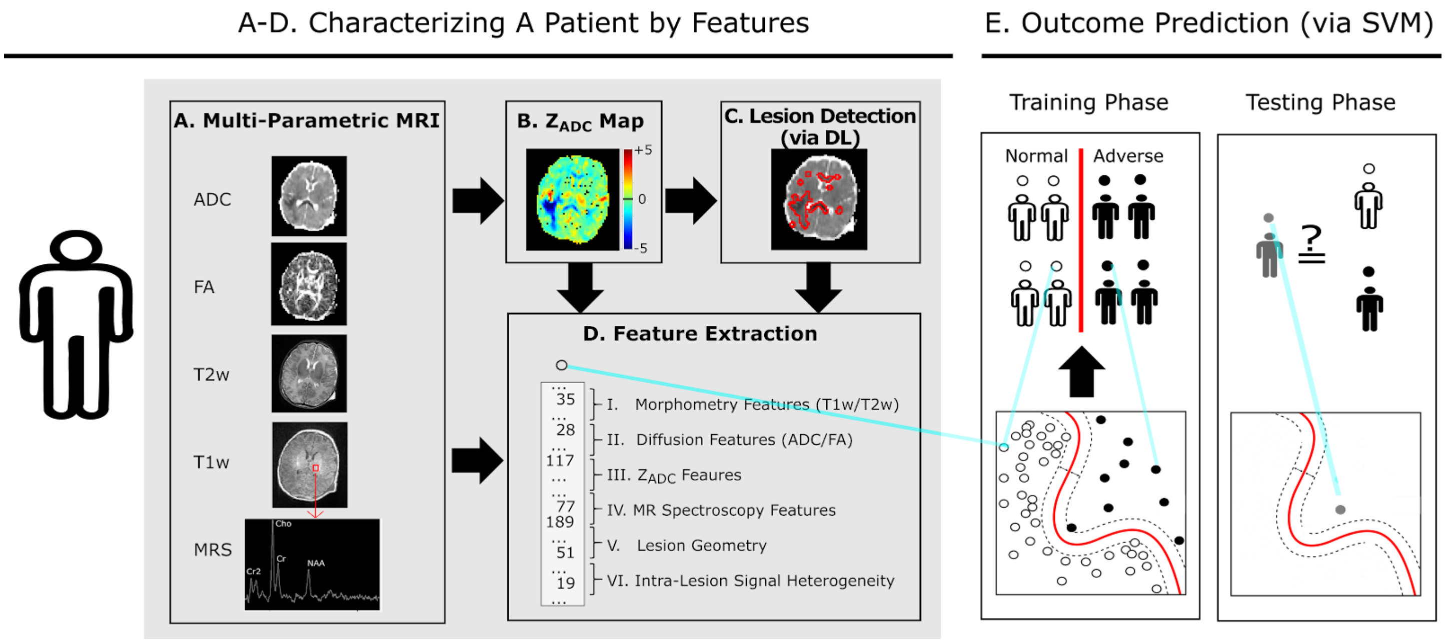
FRONTIERS IN MEDICINE

Machine Learning in Medicine

Alvin Rajkomar, M.D., Jeffrey Dean, Ph.D., and Isaac Kohane, M.D., Ph.D.

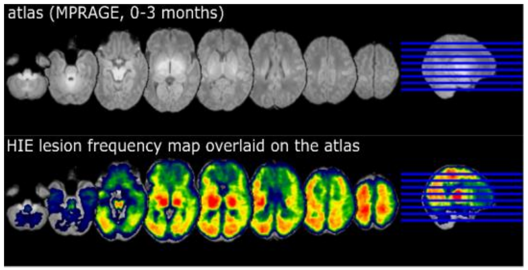
Rajkomar A, Dean J, Kohane I. Machine Learning in Medicine. New England Journal of Medicine. 2019;380(14):1347-1358. doi:10.1056/NEJMra1814259

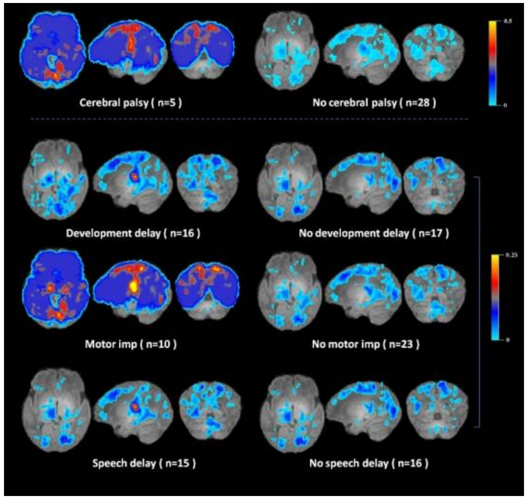
Proposed Framework Example: Unpublished Work



Data-Driven Outcome Prediction

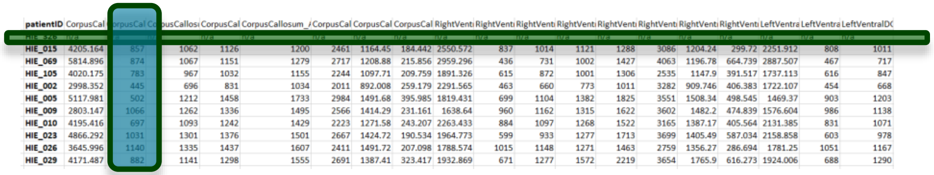
- Lesion-Symptom





- Radiomics <u>without</u> lesion segmentation

Feature
(histogram analyses, heterogeneities, volume, geometry… of each of 62 structures)



patientID	CorpusCal	CorpusCal	CorpusCallos	CorpusCal	CorpusCallosum_/	CorpusCal	CorpusCal	CorpusCal	RightVent	RightVent	RightVent	RightVent	RightVent	RightVent	RightVent	RightVent	LeftVentra	LeftVentra	LeftVentralDC
HIE_326	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HIE_015	4205.164	857	1062	1126	1200	2461	1164.45	184.442	2550.572	837	1014	1121	1288	3086	1204.24	299.72	2251.912	808	1011
HIE_069	5814.896	874	1067	1151	1279	2717	1208.88	215.856	2959.296	436	731	1002	1427	4063	1196.78	664.739	2887.507	467	717
HIE_105	4020.175	783	967	1032	1155	2244	1097.71	209.759	1891.326	615	872	1001	1306	2535	1147.9	391.517	1737.113	616	847
HIE_002	2998.352	445	696	831	1034	2011	892.008	259.179	2291.565	463	660	773	1011	3282	909.746	406.383	1722.107	454	668
HIE_005	5117.981	502	1212	1458	1733	2984	1491.68	395.985	1819.431	699	1104	1382	1825	3551	1508.34	498.545	1469.37	903	1203
HIE_009	2803.147	1066	1262	1336	1495	2566	1414.29	231.161	1638.64	960	1162	1315	1622	3602	1482.2	474.839	1576.604	986	1138
HIE_010	4195.416	697	1093	1242	1429	2223	1271.58	243.207	2263.433	884	1097	1268	1522	3165	1387.17	405.564	2131.385	831	1071
HIE_023	4866.292	1031	1301	1376	1501	2667	1424.72	190.534	1964.773	599	933	1277	1713	3699	1405.49	587.034	2158.858	603	978
HIE_026	3645.996	1140	1335	1437	1607	2411	1491.72	207.098	1788.574	1015	1148	1271	1463	2759	1356.27	286.694	1781.25	1051	1167
HIE_029	4171.487	882	1141	1298	1555	2691	1387.41	323.417	1932.869	671	1277	1572	2219	3654	1765.9	616.273	1924.006	688	1290

patient

Features selected by our algorithm

For Cerebral Palsy
- AnteriorLimbICleft_ADC_p0

For Visual Impairment
- ParietalLateralGMRight_ADC_p25
- PLICLeft_ADC_stdev

For Dev. Delay
- aed_discharge__2
- aed_discharge__1
- AnteriorLimbICleft_ADC_p25
- aed_discharge__3
- aed_discharge__4
- RightInsula_ADC_p100
- OccipitalMedialGMLeft_ADC_stdev

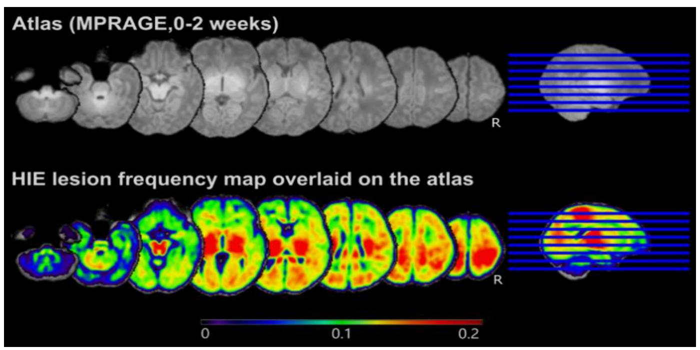
For Hearing Impairment
- TemporalInferiorGMRight_ADC_p0
- Vermis_ADC_mean
- PLICLeft_ADC_p75

Honorable Mention; Pilot Funding Finalist
MGHfC Research Day, 2018

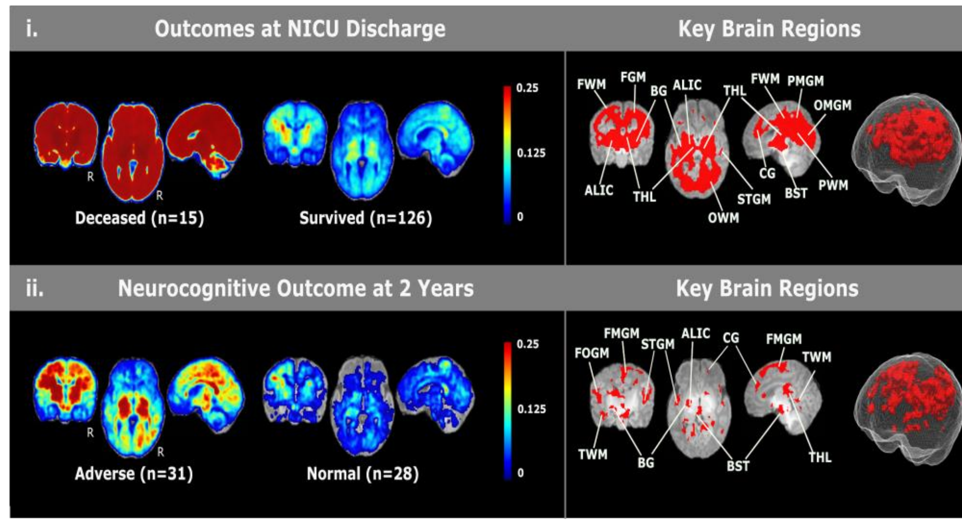
Potential of Machine Learning Outcome Prediction

What about Other Locations?

Our preliminary results show
a) vulnerability throughout the brain
b) vulnerability varying from voxel by voxel



Song, …, Grant, Ou, PAS, 2019
Song, …, Grant, Bates Ou, under review, 2019



Voxel-wise Liebermeister test
P<0.05 after 10000 permutations and multi-comparison correction
Controlling for covariates (age, sex at MRI, treatment, lesion volume)

Data-Driven Outcome Prediction *Example*

- Can an early MRI (first 1-2 weeks of life) predict which infants will be diagnosed with CP?

Outcome	Accuracy	AUC	Sensitivity	Specificity
Developmental Delay	0.682	0.725	0.800	0.583
Cerebral Palsy	**0.952**	**0.974**	**1.00**	**0.947**

- The accuracy of predicting outcomes at age 2 years was 68% for developmental delay (sensitivity 0.9, specificity 0.5) and 95% for CP (sensitivity 1, specificity ~0.95).

Can these methodologies be applied to other "high-risk," complex neonatal cohorts (e.g. Opioid exposure)???

MassGeneral Hospital for Children
INFANT BRAIN CENTER

- About Us
- Our Team
- Collaborating Programs
- Conditions We Treat ›
- Research
- Conferences & Events
- Patient Stories
- Support Us

Conditions We Treat

- Neonatal Seizures
- Hypoxic Ischemic Encephalopathy
- White Matter Injury
- Infant Brain Malformations
- Intraventricular Hemorrhage
- Neurogenetic Disorders
- Neuromuscular Disorders
- Congenital Infections
- Neonatal Abstinence Syndrome

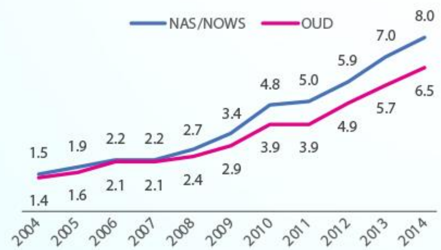
MRI imaging pipelines are being developed to better identify infants in these cohorts and detect abnormalities with the ultimate goal to improve outcomes

DRAMATIC INCREASES IN MATERNAL OPIOID USE DISORDER AND NEONATAL ABSTINENCE SYNDROME

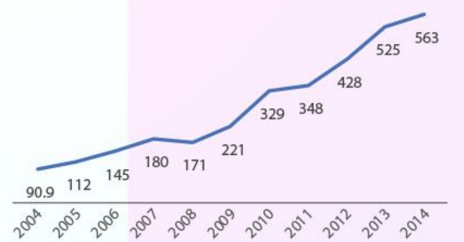
Opioid use during pregnancy can result in a drug withdrawal syndrome in newborns called **neonatal abstinence syndrome**, or **neonatal opioid withdrawal syndrome** (NAS/NOWS), which causes **costly** hospital stays. A recent analysis showed that an estimated **32,000** babies were born with this syndrome in the United States in 2014, a more than **5-fold increase** since 2004.

EVERY ~ 15 MINUTES, A BABY IS BORN SUFFERING FROM OPIOID WITHDRAWAL.

NAS/NOWS and Maternal Opioid Use Disorder on the Rise
Rates per 1,000 Hospital Births



Growing Hospital Costs for Treatment of NAS/NOWS
Inflation-Adjusted U.S. Dollars (millions)



Honein et al. Pediatrics 2019, Winkelman et al. Pediatrics 2018, Haight et al. MMWR 2018.

NIH National Institute on Drug Abuse

DRUGABUSE.GOV

Prevalence of NAS/SEN in the Commonwealth

- The rate of reported prenatal opiate exposure in Massachusetts rose from **2.6 per 1,000 hospital births in 2004 to 14.7 in 2013, an increase of more than 500%**
- However, based on hospitalization figures, researchers estimated a higher rate: that **more than 1,300 Massachusetts babies or about 17.5 per 1,000 hospital births** were born with heroin and other opioids in their system in 2013.
- Nationally, the figure is **five babies out of every 1,000 births**
- The New England region (of which Massachusetts is the most populous) has the **second highest rate of prenatal exposure in the nation** (13.7 per 1,000), after the East/South Central region
- The average length of stay in Massachusetts for an infant requiring treatment for NAS is **19 days, with an average cost (2013) of $30,000**

Franca UL, Mustafa S, McManus ML. The growing burden of neonatal opiate exposure on children and family services in Massachusetts. Child Maltreatment. 2016 Feb;21(1):80-4.
Boston Globe, Drug addicted babies in Massachusetts are triple national rate. June 19, 2014, https://www.bostonglobe.com/news/nation/2014/06/18/massachusetts-infants-born-with-opiates-system-three-times-national-rate-analysis-finds/wmfYrNDnWl8nposyOi9mCK/story.html.
Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. Journal of Perinatology. 2015 Aug;35(8):667.
Franca et al. 2016, ibid.

In-utero exposure to opioids

- Studies have shown in-utero exposure to opioids and consequent NAS is associated with long-lasting neurocognitive impairment (heterogenous cohort; many challenges)

Volumetric cerebral characteristics of children exposed to opiates and other substances in utero

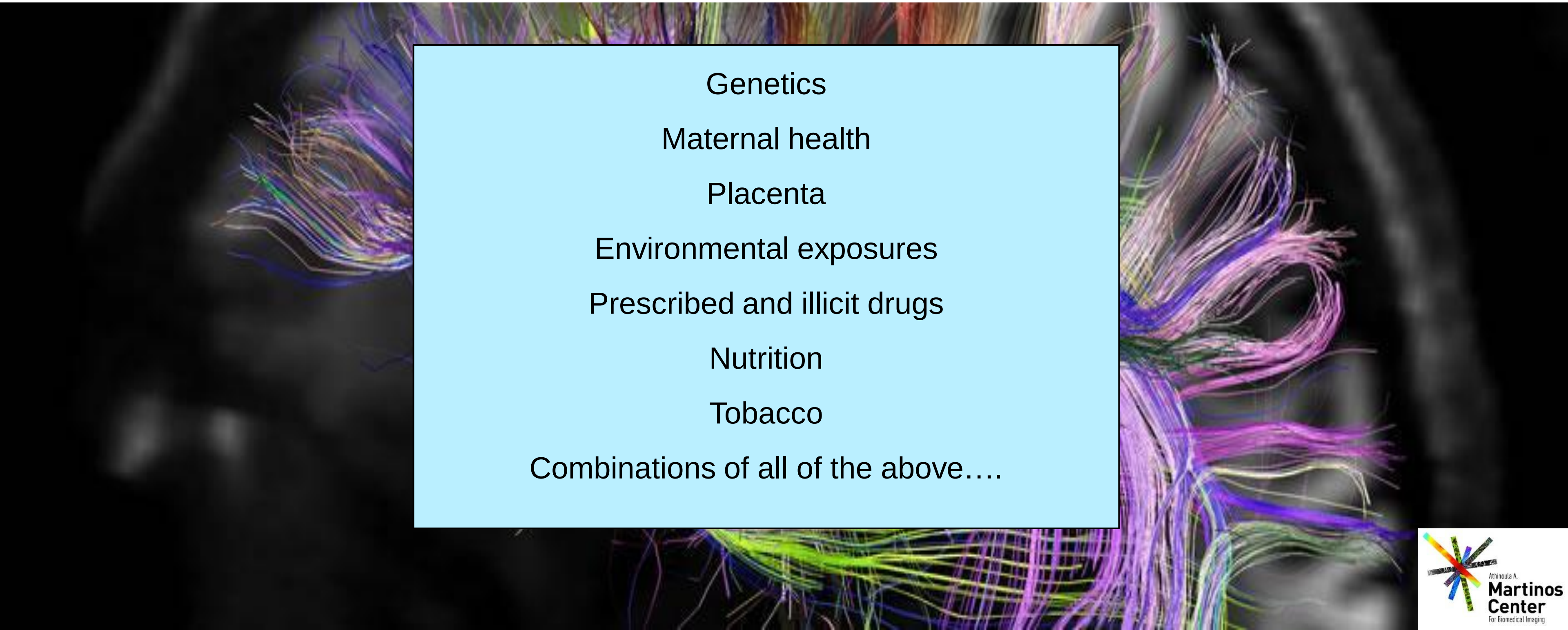
K.B. Walhovd,[a,*] V. Moe,[a] K. Slinning,[b] P. Due-Tønnessen,[c] A. Bjørnerud,[c] A.M. Dale,[d,e] A. van der Kouwe,[e] B.T. Quinn,[f] B. Kosofsky,[f] D. Greve,[e] and B. Fischl[e,g]

Neonatal Abstinence Syndrome and High School Performance

Ju Lee Oei, MD,[a,b,c] Edward Melhuish, PhD,[d,e,f] Hannah Uebel,[a] Nadin Azzam,[a] Courtney Breen, PhD,[g] Lucinda Burns, PhD,[g] Lisa Hilder, MBBS,[h] Barbara Bajuk, MPH,[i] Mohamed E. Abdel-Latif, MD,[j,k] Meredith Ward, FRACP,[a,b] John M. Feller, FRACP,[a,l] Janet Falconer, CNC,[m] Sara Clews, CNC,[m] John Eastwood, FRACP, PhD,[a,c,n,o,p] Annie Li,[a] Ian M. Wright, FRACP[d,q,r]

Hamilton R, McGlone L, MacKinnon JR, *et al.* Ophthalmic, clinical and visual electrophysiological findings in children born to mothers prescribed substitute methadone in pregnancy. *British Journal of Ophthalmology* 2010;**94:**696-700.

Potential mechanisms for abnormal fetal brain development are complex and multifactorial



Genetics

Maternal health

Placenta

Environmental exposures

Prescribed and illicit drugs

Nutrition

Tobacco

Combinations of all of the above….

Timing

- Fetal effects of exposures during pregnancy
- Timing of initial exposure
- Dose; Length of exposure
- Ex FASD, SSRI, anti-epileptics etc.

606 **Prenatal Development**

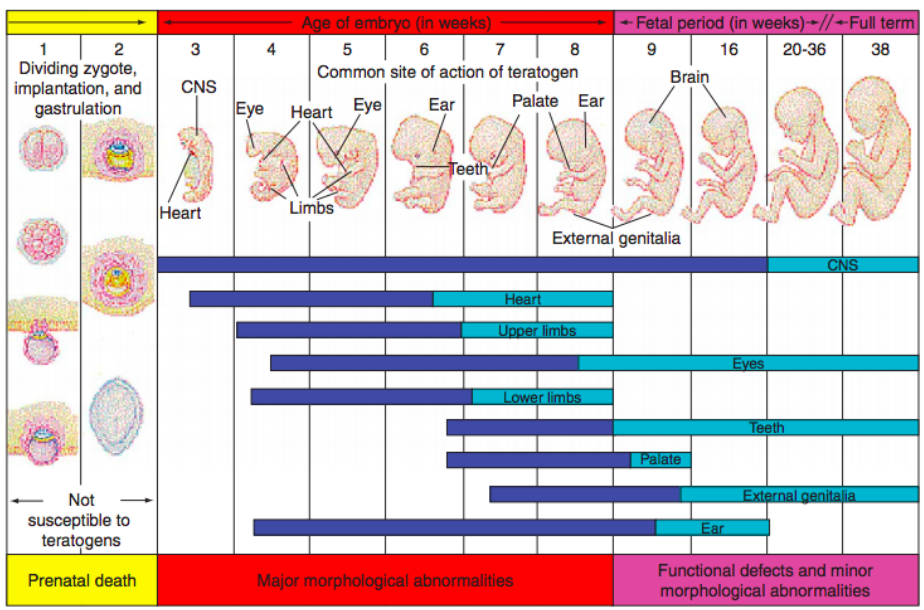


Figure 1 Schematic representation of growth and development during gestation. Reproduced from Moore KL and Persaud TV (1993) *The Developing Human: Clinically Oriented Embryology*, 5th edn. Philadelphia: W.B. Saunders Company, with permission from Elsevier. CNS, Central Nervous Systems.

Lewis Ball Holmes, MD
•Emeritus Unit Chief, Medical Genetics, Pediatric Service
•Emeritus Director, Genetic Counseling & Screening Services,
•Perinatal Diagnostic Unit, Obstetrics Program

Maternal Infant NeuroDevelopment Study

Can these methodologies be applied to other "high-risk," complex neonatal cohorts (e.g. Opioid exposure)???

↓

K12 Career Development Program in Substance Use and Addiction Medicine (MGH)

↓

Maternal Infant NeuroDevelopment Study (MINDS)

NIH National Institute on Drug Abuse

Research reported in this portion of the talk] was supported by The National Institute of Drug Abuse of the National Institutes of Health under award number **K12 DA043490-01.** The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

Abbreviated Specific Aims

- Aim 1: Characterize regional brain volumes and structural/functional connectivity patterns in opioid-exposed neonates compared to age- and sex-matched healthy control infants.
- Aim 2: Characterize the relationship between imaging findings and neurodevelopmental outcomes assessed with the Bayley-III Scale in opioid-exposed neonates between 18 and 24 months.

- Can we create a research imaging pipeline at MGH for infants with in-utero drug exposure(s)?
- Maintain our practices of: reducing stigma, partnering with parents, & advocating to maximize brain health for all of our patients

Boston Children's Hospital
Until every child is well

Team Effort

MassGeneral for Children

MINDS CONTACT LIST Last updated 3/29/19

Name	Role in study	Department or Division	Phone Number	Email Address	MINDS e-mail?	Notes
Bates, Sara V.	Principal Investigator	Newborn Medicine	W: 617-724-9040 M: 617-851-7474	sbates@mgh.harvard.edu	Yes	On IRB
Bell, Janet	Attending RN, Ellison 13	Newborn Medicine	W: 617-724-6753	JBELL2@PARTNERS.ORG	Yes	
Bernstein, Sarah	Consultant					HOPE Clinic
Buch, Karen	Attending Neuroradiologist					
Cahill, Kellie	MR Operations Manager*					
Caruso, Paul	Director, Pediatric Neuroradic					
Clark, Maureen	Sr. Research Manager					On IRB
Desmond, Erin Manley, Meghan	MRI Supervisors					Page when enrolled patient to schedule scan time
Donohue, Teresa	MR Technologist					
Evins, Eden	K12 PI					Center for Addiction Medicine (CAM)
Foster, Christine	MR Technologist					
Francis, Kim	Nursing Director, Ellison 13					
Gagoski, Borjan	Co-investigator					
Gee, Michael	Chief, Pediatric Radiology					
Geha, Mayya	Co-investigator					On IRB
Gilman, Jodi	K12 Mentor					On IRB; Center for Addiction Medicine (CAM)
Golub, Randy	Co-investigator					On IRB; Mentor
Grant, Ellen	Co-investigator					On IRB; Mentor
Guidoboni, Lindsey	MR Technologist					
Kaimal, Anjali	Consultant					
Kerzner, Leslie	Co-investigator					On IRB
Kirsch, John	Chief, MR Physicist					
Kuehn, Devon	Consultant					Vice Chair of Reseach East Carolina Univ
Larou, Paul	Co-investigator					On IRB
MacDonald, Roseanne	MR Technologist					
[illegible], Juan	Co-investigator					On IRB
Milbury, Carol	Grants Management					
Ou, Yangming	Co-investigator					On IRB
Pachas, Gladys	K12 Manager					
Peccei, Alexandra	Consultant					
Perkins, David	Grants Management					
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Ratai, Eva	Consultant					MR Spectroscopy
Ricevuto, Christopher	Grants Management					
Rich, Karen	MRI Research Technologist					
Rigotti, Nancy	Principal Investigator K12 Fu					Fund # 231440
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Zollei, Lilla	Consultant	Radiology	W: 617-643-7791		No	Martinos Center; Computational Neuroimaging

MR Operations
MR Physicists
MR technologists
Neuroradiology
Neurology
Nursing
OBGYN
OT/PT/Nutrition
Pediatrics
Psychiatry
Placenta Pathology
Social Work

Maternal Infant NeuroDevelopment Study

Inclusion & Exclusion Criteria

Inclusion

Exposed Infants:

- Newborns ≥ 35 weeks gestational age
- Known in-utero exposure to opiates (e.g. mother has been in recovery and on medication assisted therapy (MAT) during pregnancy and/or is using illicit opiates). This information will be extracted from the EHR. In the event any clarification is required, the PI will contact the primary OBGYN for additional information.
- Postnatal diagnosis of NAS, NOWS, or drug withdrawal syndrome

Control Infants:

- Newborns ≥ 35 weeks gestational age born at MGH
- No diagnosis of NAS, NOWS, drug withdrawal syndrome, or history of in-utero exposure to drugs.
- No maternal history notable for OUD and/or a negative toxicology screen
- No maternal history of any of the following prescribed or illicit exposures during pregnancy: opioids (prior to the onset of labor), anti-epileptics, alcohol consumption, tobacco or marijuana use. This information will be abstracted from the EHR.

Exclusion

Exposed and Control Infants:

- Known chromosomal or major congenital abnormalities
- Suspected in-born error of metabolism
- Brain insult or injury (e.g. Hypoxic ischemic encephalopathy, perinatal stroke)
- Sepsis
- Respiratory distress or failure requiring mechanical ventilator support
- Presence of electrically, magnetically, or mechanically activated medical implants (such as cardiac pacemakers)
- Maternal history of major neuropsychiatric illness such as psychosis, bipolar or schizophrenia
- In the opinion of the PI, not able to safely participate in this study

General Study Overview

- Clinical data collected from EHR:
  - Mom
  - Infant
  - Placenta
- REDCap

Pregnant mothers will be identified through collaboration with the OB and Neonatology teams

↓

Consent AFTER infant is delivered

↓

Enrolled infants meeting all inclusion criteria are scanned within the first 3 weeks of life

↓

Bayley 3 Scales of Toddler and Infant Development obtained in follow-up clinic at 12 and 24 months of age PER CLINICAL ROUTINE

The HOPE Clinic (Harnessing support for Opioid and substance use disorders in Pregnancy and Early childhood) at Massachusetts General Hospital

Maternal Infant NeuroDevelopment Study

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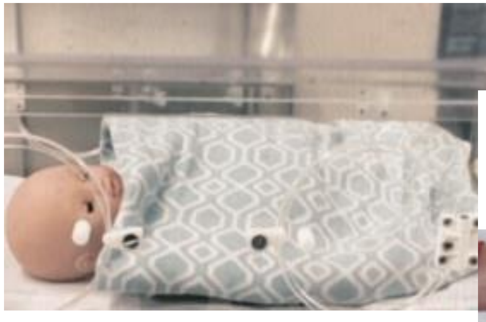
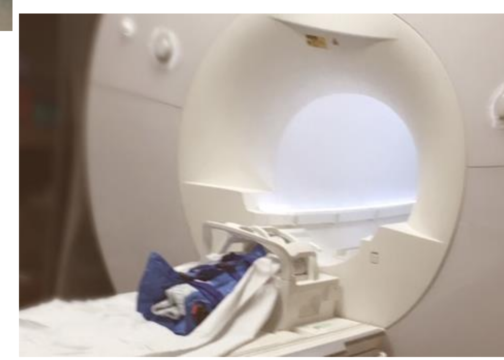
3T Scanner

MassGeneral for Children





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MINDS imaging protocol (~45 minutes)

Sequence	Average Time (minutes)
Localizer	
mocoMEMPRAGE (T1w with prospective motion correction)	5
SMS diffusion weighted imaging with two b shells, and bmax = 2000	5-7
Sagittal T2	3
Spectroscopy	5
SMS resting state fMRI (BOLD)	10
Axial T2	5
SWI	5

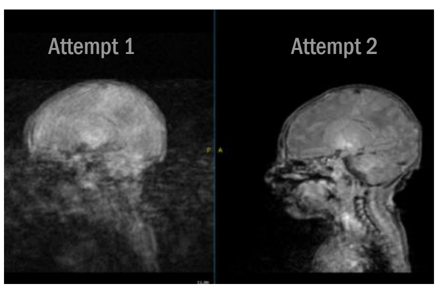
Maternal Infant NeuroDevelopment Study

Processing Workflow Overview

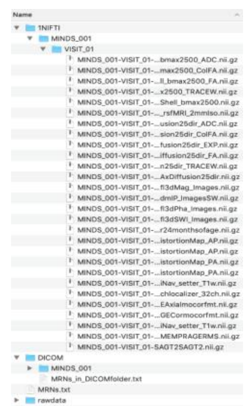
DICOM Review
- Remove images with motion artifact

Transfer to cluster
- Preprocessing

Data Analysis
- Structural
- Resting state
- Diffusion/Tractography



MINDS_001: MPRAGE with motion artifact (left) and without (right)



- Renaming/organizing files
- mri_convert dicom → niftii

L. Zöllei, I. Filipiak, E. Saliba, L. Barantin, C. Destrieux, H. Dupuis, M. Cottier, J. Owen, Y. Ou, A. Varjabedian, C. Jaimes, E. Grant, and A. Yendiki. 2016. **"A novel automated probabilistic tractography tool with anatomical priors for use in the newborn brain**

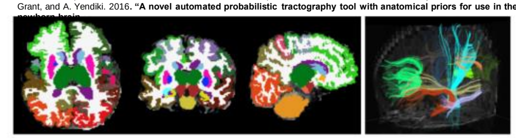
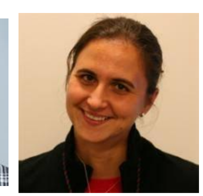
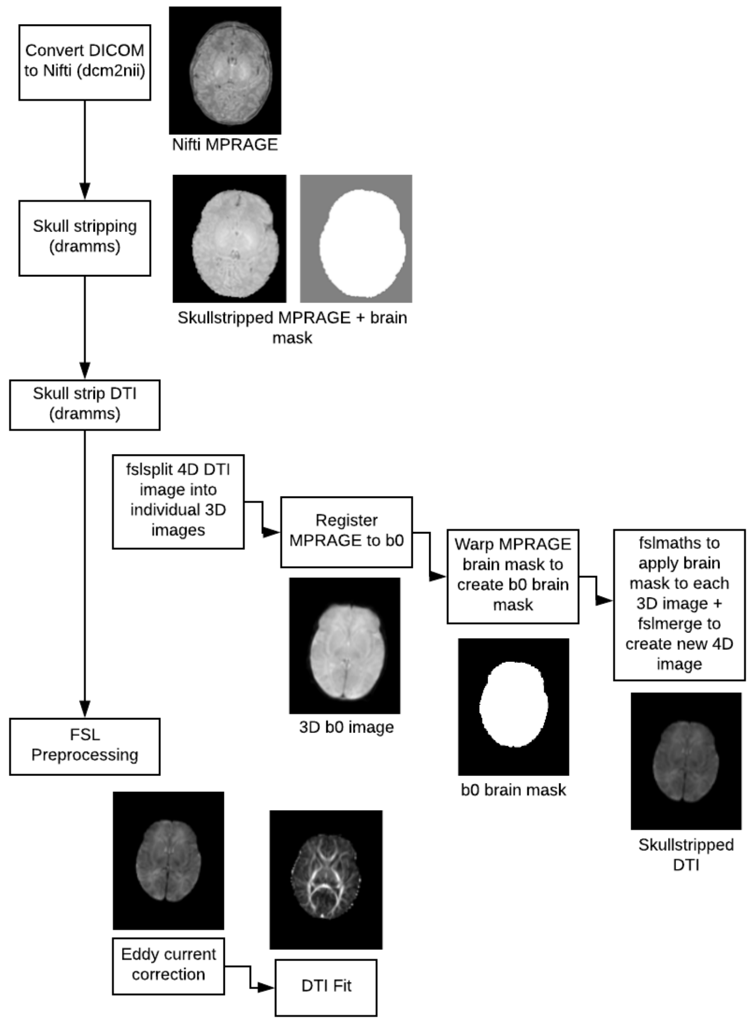


Fig. 1. (**Left**) Cortical and subcortical segmentation labels displayed on the structural MRI of an infant. (**Right**) Manually annotated tracts of a sample subject: CST (light blue), FMIN (green), FMAJ (bright green), IFOF (beige), ILF (purple), UF (red) and SLF (light brown).



Maternal Infant NeuroDevelopment Study

Detailed DTI pre-processing workflow



*Currently processing initial group of patients; unpublished data

Maternal Infant NeuroDevelopment Study

BRIGHAM AND WOMEN'S HOSPITAL

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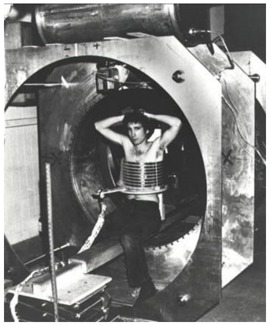
40 Years Later…

MassGeneral for Children

Athinoula A. Martinos Center for Biomedical Imaging

Indomitable



MRI compatible isolette (early example)

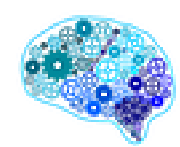
Embrace: Aspect Imaging

Neuro Optics: NIRS + DCS

Baby Connectome

NIH: Human placenta project

Optimization of acquisition and processing



fMRI (stim, resting state)

Fetal-Neonatal Neuroimaging Developmental Science Center

*So many more amazing scienctific discoveries and technological advances…far to many to list

Future Directions

- Despite limitations, the machine learning algorithms presented provide promising first steps in both detecting lesions and predicting outcomes
- Increasing our inputs/features → clues → improved learning/outputs
- Continue to explore mechanisms
- Integration of clinical data (ongoing)
- Continue to build collaborative, multi-site, multidisciplinary research teams

Learning Objectives

- During patient case discussions, appreciate both the strengths and limitations of MRI

Focus: HIE

- Reflect upon the role of MRI in difficult diagnostic and therapeutic decisions
- Describe the technology and potential applications of machine learning algorithms in neonatal neuroimaging

Ex. HIE & NAS

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Janet Soul, MD

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Duke:

Michael Cotten, MD

Monica Lemmon, MD

Women & Infants:

Abbot Laptook, MD

East Carolina University:

Devon Kuehn, MD

Imperial College London:

Sudhin Thayyil MD, PhD

Children's Hospital Los Angeles:

Ashwini Lakshmanan MD, MPH

Special thanks to the patients & families we have the privilege of caring for

MassGeneral Hospital for Children

HARVARD MEDICAL SCHOOL

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NIH National Institute on Drug Abuse

Maternal Infant NeuroDevelopment Study

Contacts & Image Processing Links

Additional questions, comments, ideas about potential collaborations???
Please reach out; we'd love to hear from you!

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- Yangming Ou yangming.ou@childrens.harvard.edu
  Image processing & algorithm development

- https://www.nitrc.org/projects/normalizefov
- https://www.nitrc.org/projects/picasso
- https://www.cbica.upenn.edu/sbia/software/MUSE
- https://www.nitrc.org/projects/dramms
- https://www.cbica.upenn.edu/sbia/software/dramms/tools/ravens.html
- https://www.nitrc.org/projects/popdramms
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