# Evaluation of White Matter in Preterm Infants With Fetal Growth Restriction

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HARVARD MEDICAL SCHOOL

# Road Map

- Introduction
- Material and Methods
  - DTI Atlas for Group Comparison
  - Towards a Robust Group Comparison
- Results
- Conclusion

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# Introduction

- Fetal Growth Restriction (FGR)
  - Weight below 10$^{th}$ percentile of normal weight for gestational age
  - Often caused by placental function disruption
  - Often linked to prematurity
  - Occurs during accelerated brain development
- Prematurity and FGR may lead to disabilities
  - Motor skills, cognitive function
  - Lower neurodevelopmental score
- Early care in the Newborn Intensive Care Unit (NICU) crucial to FGR infants development

# The NIDCAP Program

- NIDCAP = Newborn Individualized Development Care and Assessment Program

- Objectives
  - Better neurodevelopment of FGR preterm-born children
  - Support brain structure maturation

- How
  - Minimize environmental stress for the baby
  - Observation and evaluation of the infant's behavior
  - Adaptation of care to get closer to the intra-uterine environment

# Previous Study on NIDCAP

- Randomized study on 30 AGA preterm-born children
  - Two groups: 14 in standard care / 16 in NIDCAP program
  - Influence of NIDCAP on brain development

- Comparison at two time points
  - Do differences exist ? Are they maintained at a later stage ?
  - 2 weeks: comparison of DTI derived scalar parameters
  - 9 months: behavioral assessment (mental / motor scale)

- Better maturation at 2 weeks (PLIC on left side)
  - Consistent with brain functional differences
  - Lasting effects at 9 months behavioral assessment

H. Als et al. Early experience alters brain function and structure. Pediatrics 113(4):846-857, 2004.

# Challenges

- Problems
  - Scalar measures: loss of information
  - Predefined regions of interest, manually drawn
  - Movement artifacts, distortion in the images

➔ Objective: study of NIDCAP influence on white matter
  - Local and automatic evaluation over the whole brain
  - Use the whole tensor and be robust to image artifacts

- Our approach
  - Construction of an age adapted common coordinate system
  - Robust comparison of populations

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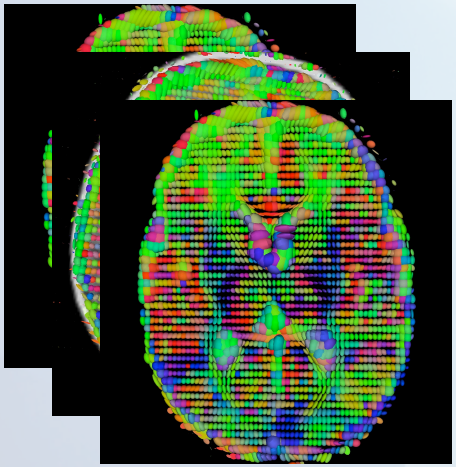
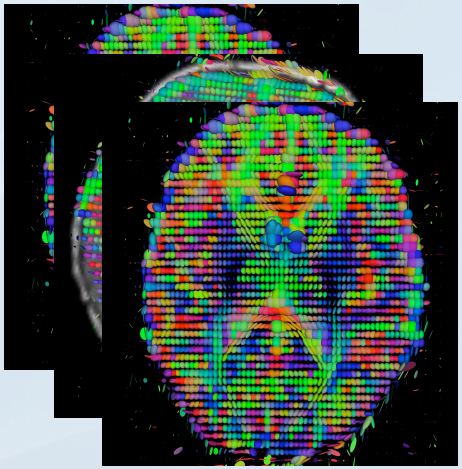
# DTI Atlas for Group Comparison

- Goal: Compare populations to detect groupwise differences



Controls Group



NIDCAP Group

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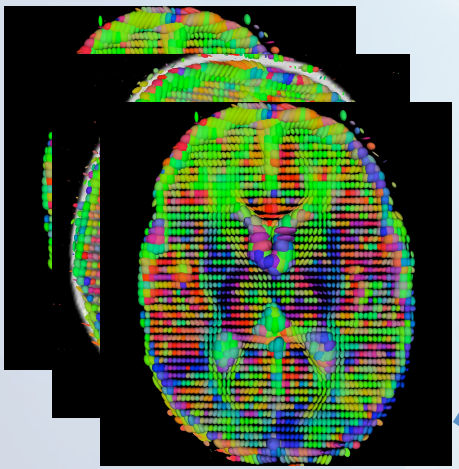

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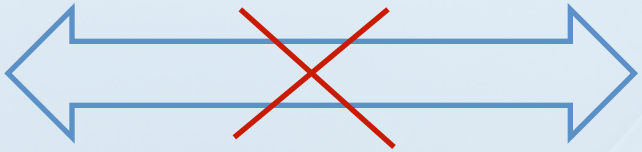
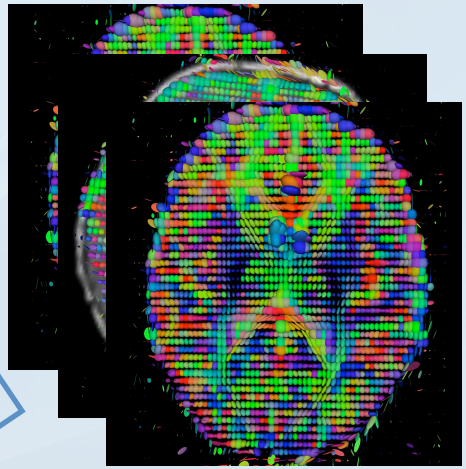
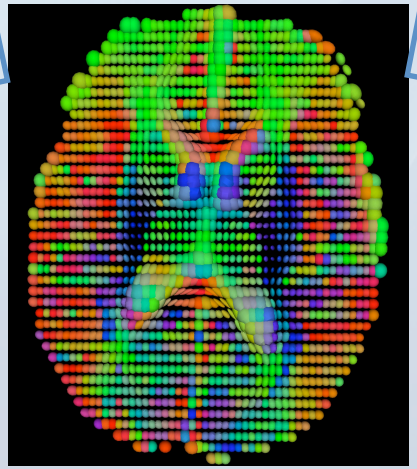




NIDCAP Group



Atlas = Common coordinate system

# Average Image Construction

- Challenges
  - Very early acquisitions (42 weeks PMA)
  - Specific anatomy → External adult reference standard not adapted
- Our approach
  - Build a geometrically unbiased DTI atlas from the populations
- Atlas construction method [Guimond et al., 2000]
  - Iteration over two steps
    - Registration of all DT images on the current reference
    - Build a new reference (from images and transformations)

[Guimond et al., 2000]: Average Brain Models: A Convergence Study, CVIU, 2000.

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# DTI Group Comparison

- Objective: Detect groupwise differences between populations
- Cramers test [Whitcher et al., 2007]
  - Use of the full tensor: Log-Euclidean distance on tensors
  - Permutation testing: No assumption on a specific PDF for the statistic


- Output: voxel-wise probability of the existence of differences

B. Whitcher et al. Statistical Group comparison of Diffusion Tensors via Multivariate Hypothesis Testing. MRM 57:1065-1074. 2007.

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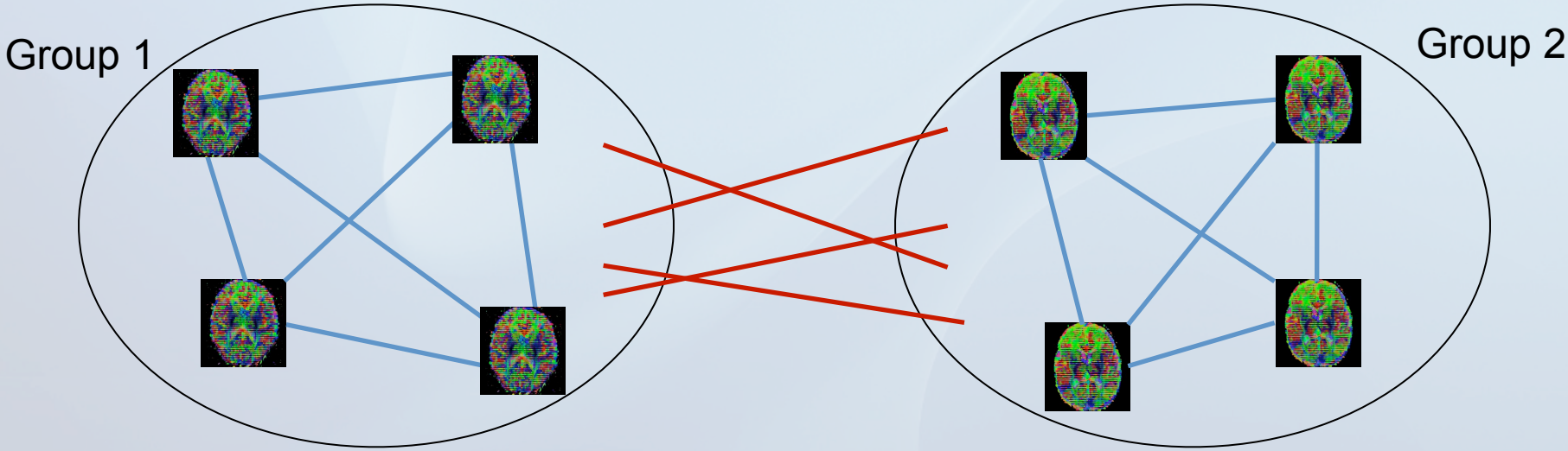


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# Robust DTI Comparison : Continuous STAPLE

- Challenges: several sources of bias in DTI comparison
  - Acquisition problems (DTI distortion, movement artifacts)
  - Registration errors

➔Need for a robust group comparison

- Continuous STAPLE [Commowick et al., 2009]
  - Input: vector images (e.g. tensors in the Log-Euclidean space)
  - EM algorithm to compute at the same time
    - Typical tensor image underlying the dataset
    - Parameters for each image: offset to the typical image and covariance matrix

[Commowick et al., 2009]: A Continuous STAPLE for Scalar, Vector and Tensor Images: An Application to DTI Analysis. IEEE TMI, 28(6):838-846, 2009.

# Local Computations for Continuous STAPLE

- Great interest of continuous STAPLE
  - Produce a robust estimation of typical tensor image
  - Parameters characterize bias in the individual images
  - Adequacy parameters may be used to compare images
- Problem: parameters are computed over the whole image
  - Need for local estimates for voxelwise comparison
- Proposed solution
  - Run STAPLE on a block around each voxel
  - Keep the parameters and reference value at center voxel
  - Allows voxelwise parameters computation

# Towards a Robust Group Comparison

- Use of local continuous STAPLE
  - Parameters should be different between groups
  - Take into account erroneous tensors
- Advantage of the Cramers test
  - May be used for any data as long as a distance can be defined
- Integrating local continuous STAPLE
  - Parameters represent multivariate Gaussians
  - Distance between multivariate Gaussians
    - [Calvo & Oller, 1991]: Analytic solution of the geodesic

Calvo, M., Oller, J. An explicit solution of information geodesic equations for the multivariate normal model. Statistics and Decisions 9, 1991.

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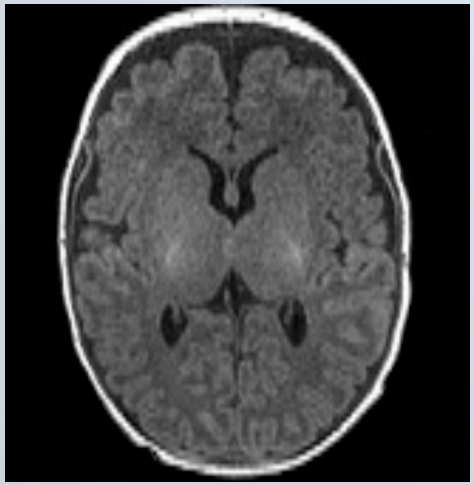
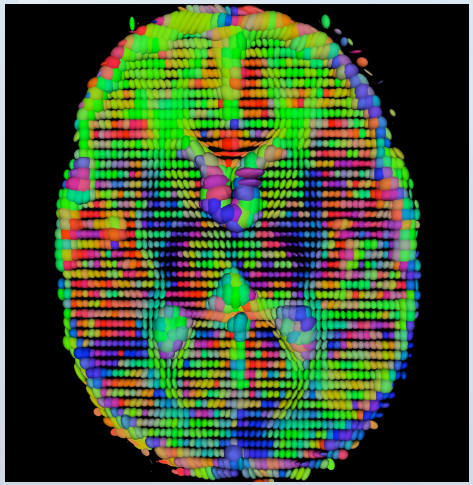
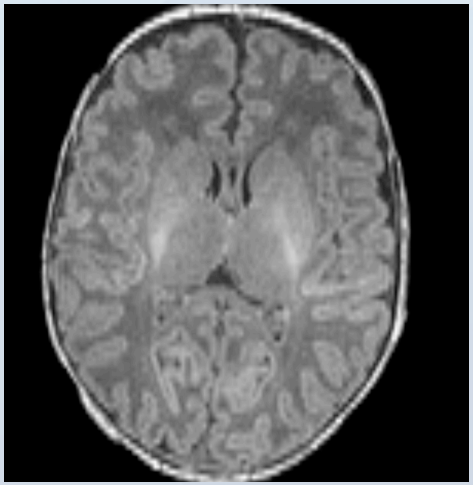
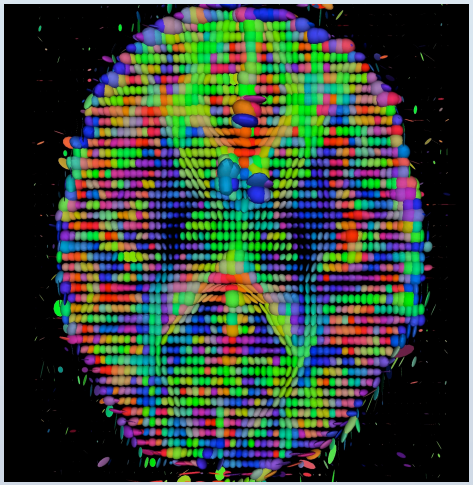
# FGR Database

- DTI Comparison at time point 2 (~ 42 weeks PMA)
  - Structural (T1, T2) acquisition (slice thicness 1.3mm)
  - DTI acquisition (between 6 and 35 directions, slice thickness 2.5mm)
  - Two groups
    - Standard care (11 infants)
    - NIDCAP group (9 infants)

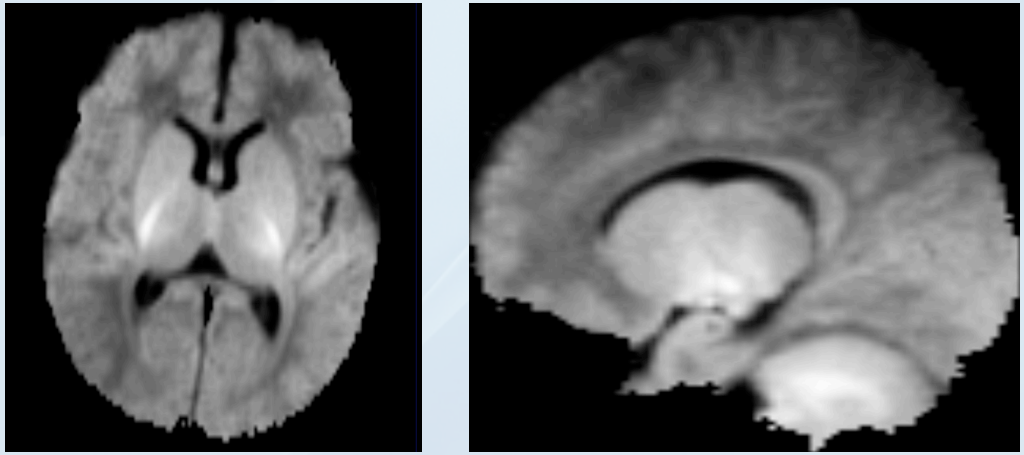
Control group infant

NIDCAP group infant

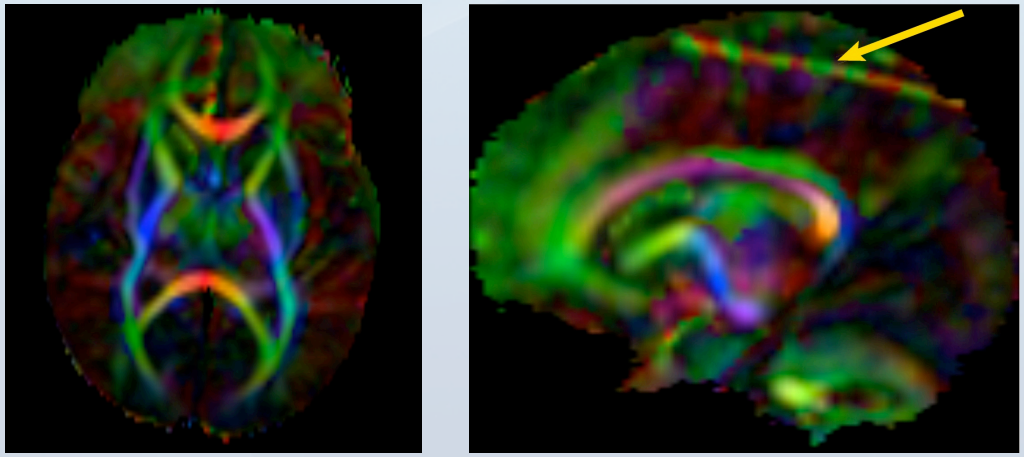
# Coordinate System Construction Results

- DTI Atlas
  - Created from 20 DTI
    - From the two groups together
- Comparison
  - Classical DTI average
  - Typical DTI Image obtained from STAPLE

➔ Illustrates STAPLE ability to handle errors



Average coordinate system anatomy



Average DTI Image

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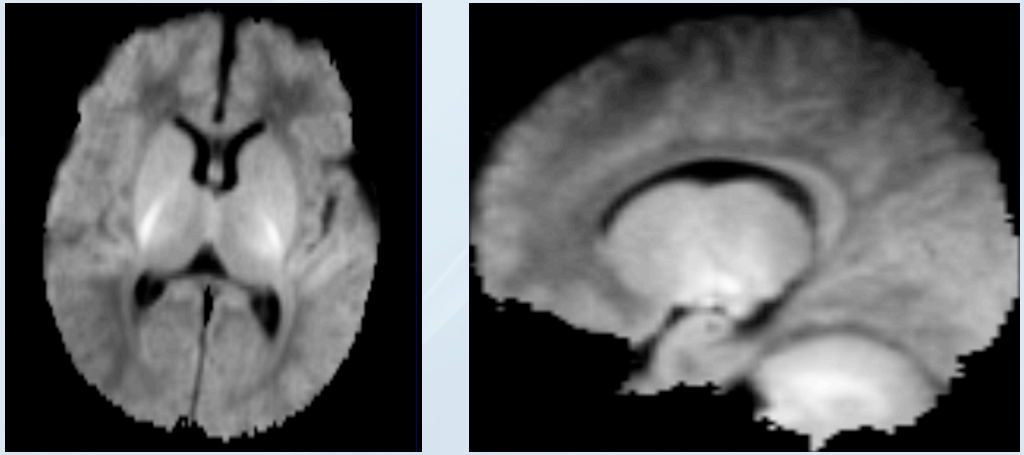

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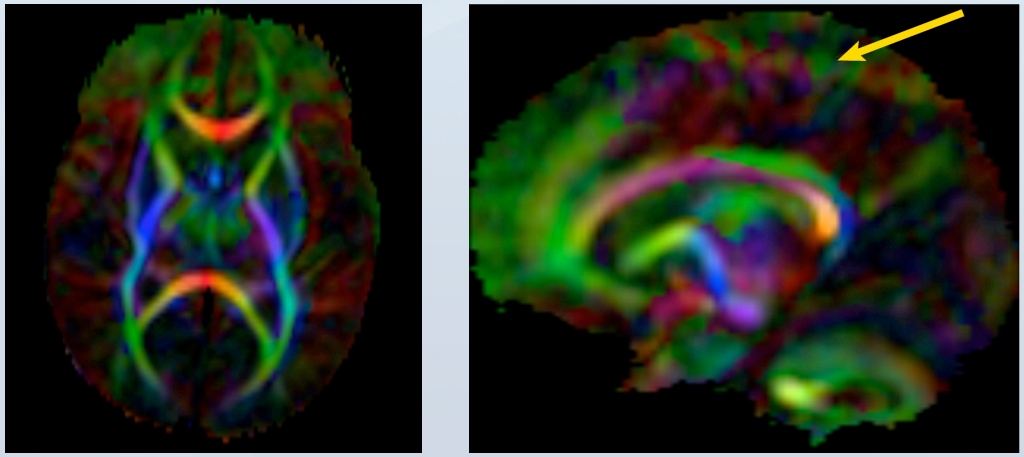
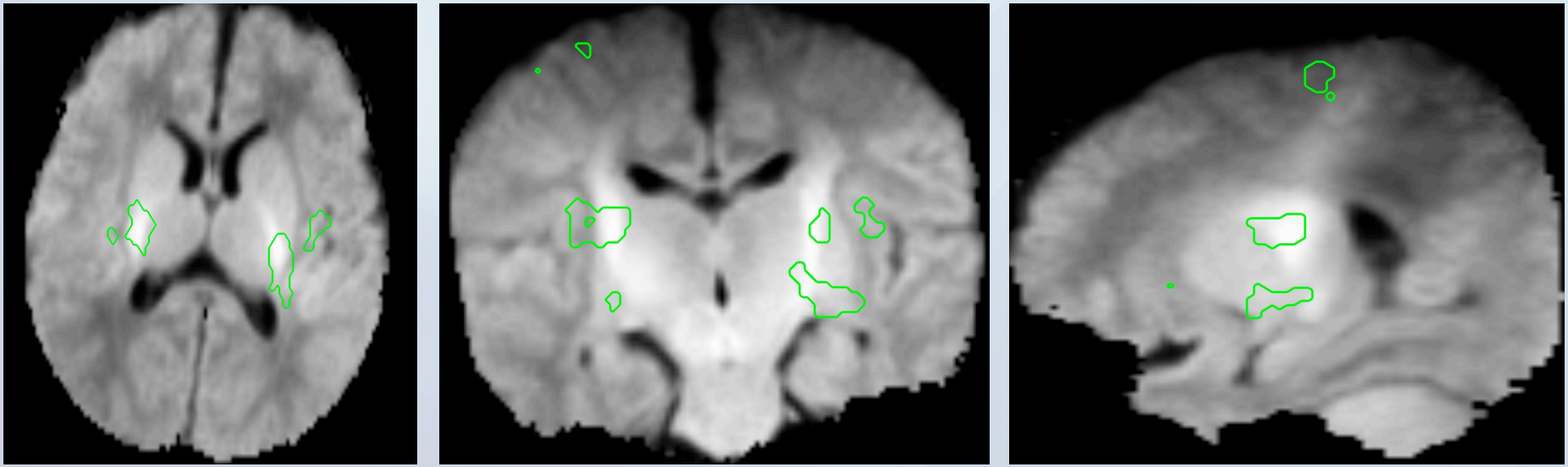


STAPLE Typical DTI Image

# Group Differences in White Matter Structure

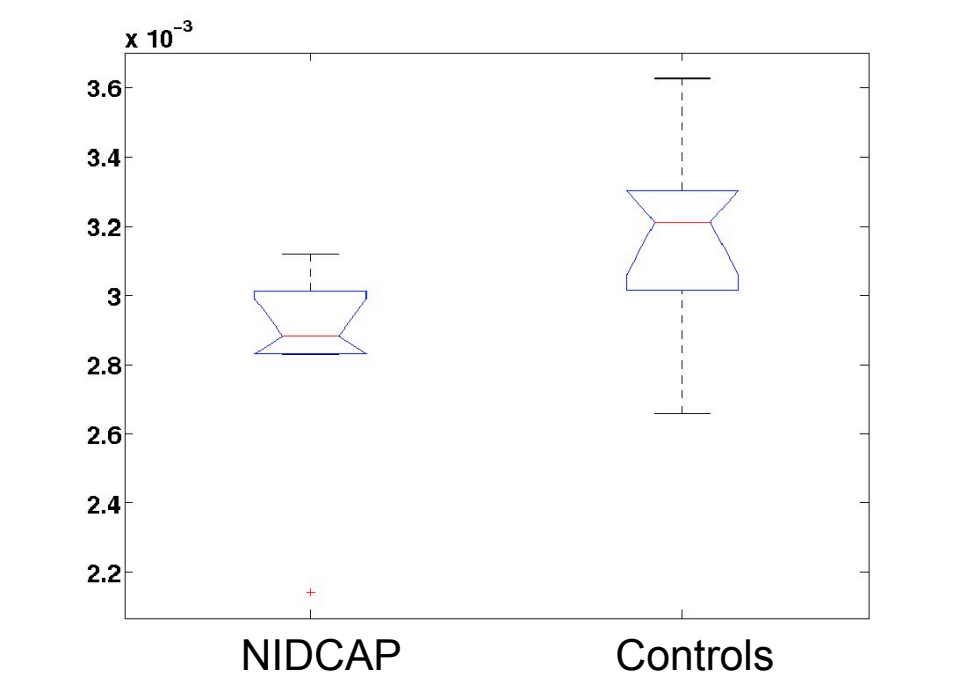
- Evaluation of WM differences
  - Differences in PLIC on both sides
  - Confirms results obtained in previous studies
  - Better detection power: differences detected on both sides



Regions different between controls and NIDCAP (95% confidence level)

# Characterization of Detected Differences

- Study of DTI derived scalar parameters
  - FA and MD values
  - ANOVA on average values
  - On detected regions
- Results
  - No difference in FA values
  - Significant difference for MD
    - Decrease in NIDCAP group




MD ANOVA Analysis

# Discussion

- Period of accelerated brain maturation
  - Premyelination period
  - Particularly in central nervous system

- Significant MD decrease in PLIC
  - Less water molecules → more structure
  - Increased premyelination in NIDCAP group

- MD decrease associated to better outcome [Krishnan, 2007]
  - Results suggest a positive impact of NIDCAP on brain development
  - Potential better outcome for the infants

M.L. Krishnan, L.E. Dyet, J.P. Boardman, O. Kapellou, J.M. Allsop, F. Cowan, A.D. Edwards, M.A. Rutherford, and S.J. Counsell. Relationship between white matter apparent diffusion coefficients in preterm infants at term-equivalent age and developmental outcome at 2 years. Pediatrics, 120(3): e604-9, 2007

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# Conclusion

- New algorithm for robust group comparison
  - DTI atlas construction
    - Adapted to the study of very young children
  - Local reference standard construction (continuous STAPLE)
    - Robust to bias sources
    - Using the whole tensor information
  - Integration of STAPLE parameters in a statistical test

- Study of white matter development in preterm FGR infants
  - Significant difference in PLIC regions on both sides
    - Decrease in MD values → better maturation in NIDCAP group
  - Potential positive influence of NIDCAP

# Perspectives

- Take into account the temporal component
  - Study at different time points
    - Are differences present before intervention ?
    - How exactly is NIDCAP influencing the development ?

- Complementary studies from other modalities
  - Comparison of structures volumes extracted from T1
  - Gyrification indexes, cortical thickness
  - Tractography studies
    - Whole brain
    - Regions with differences