DTI vs. HARDI methods in diffusion MRI: advantages and limitations in a clinical setting

Carlo Pierpaoli
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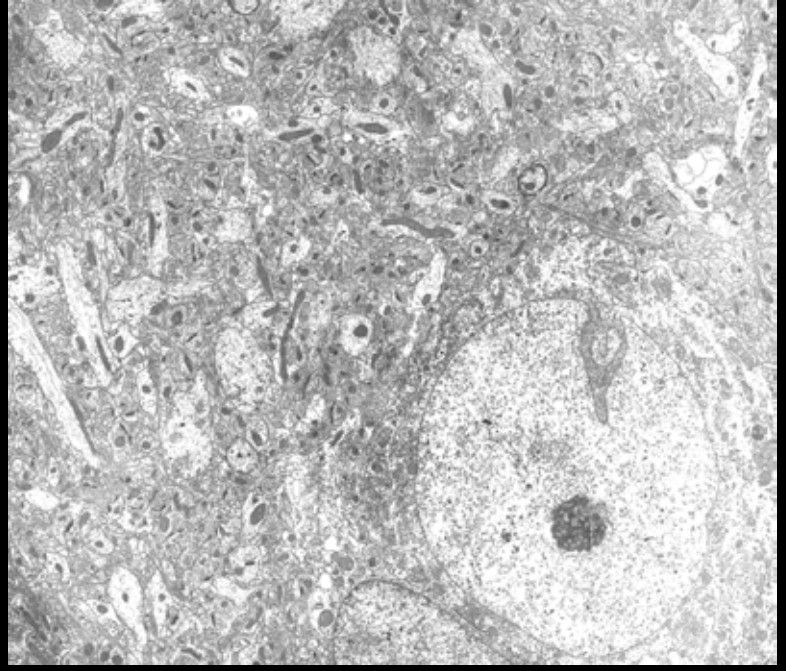
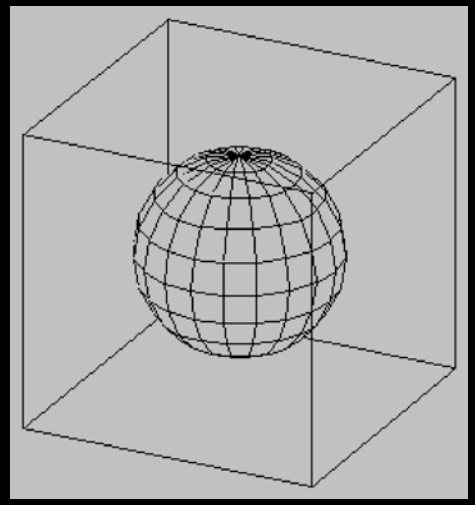
NICHD



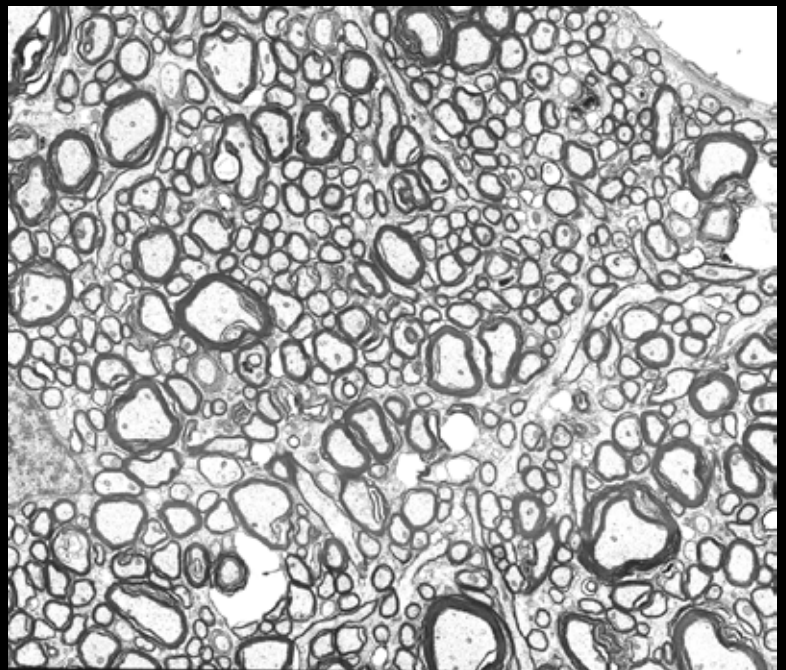
Gray matter
(Cortex)

isotropic
diffusion



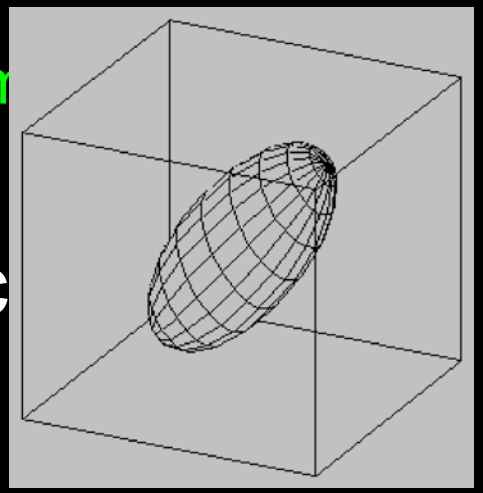
~ microns

mm



White matter
(Corpus callosum

*an*isotropic
diffusion



Poll question

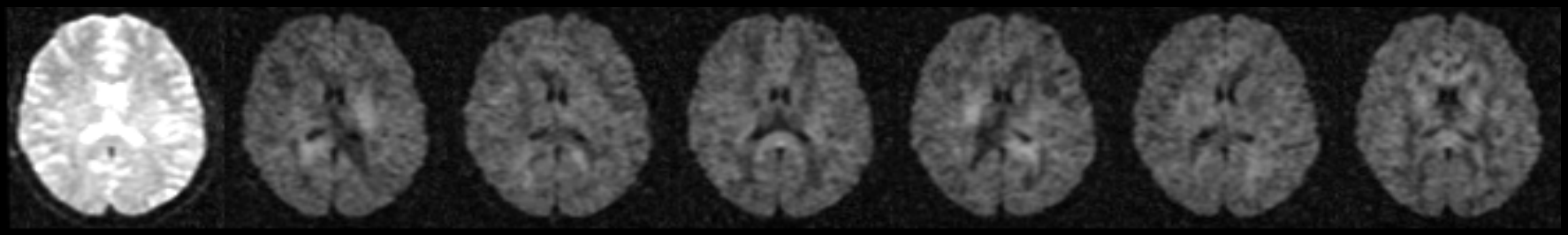
Anisotropy is related to which feature of the water displacement profile:

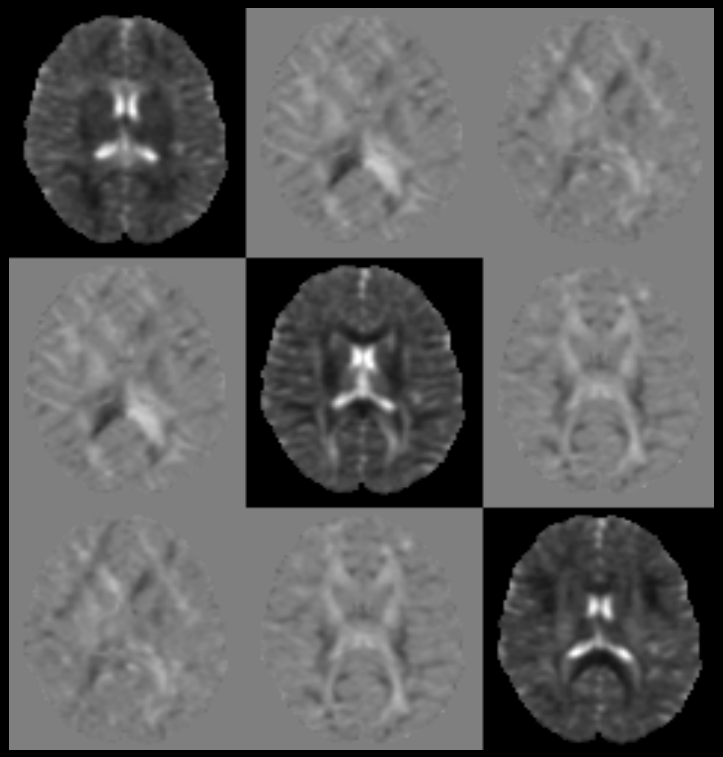
1) SIZE

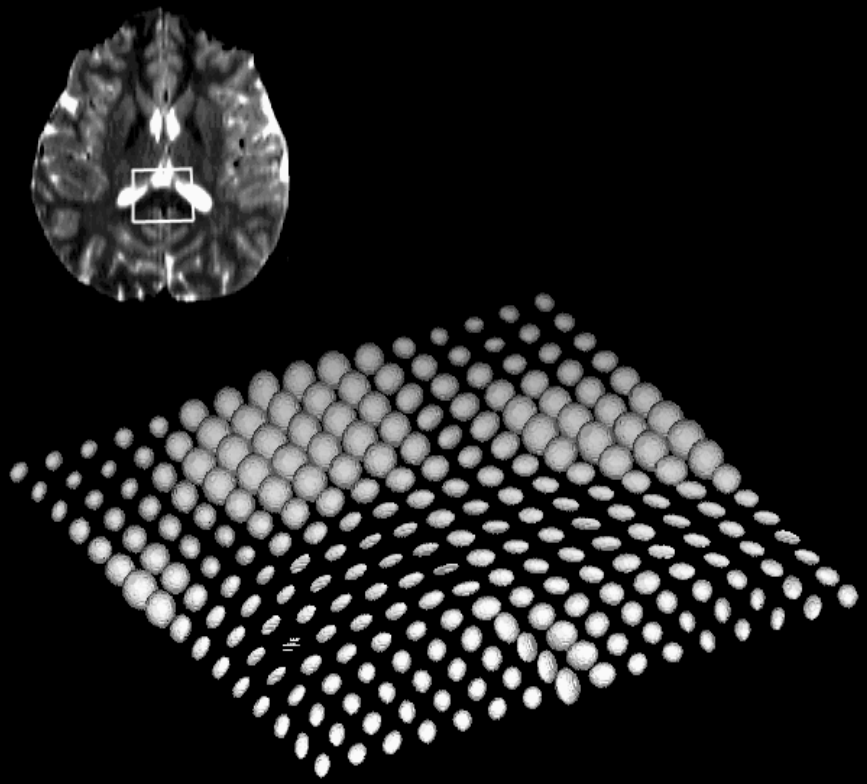
2) SHAPE

3) ORIENTATION

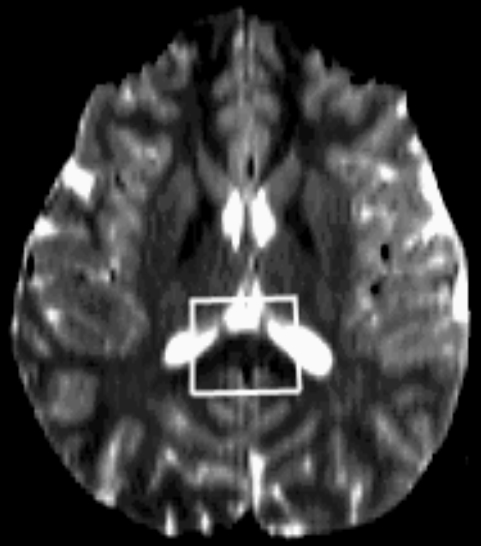
Diffusion Tensor MRI Flowchart

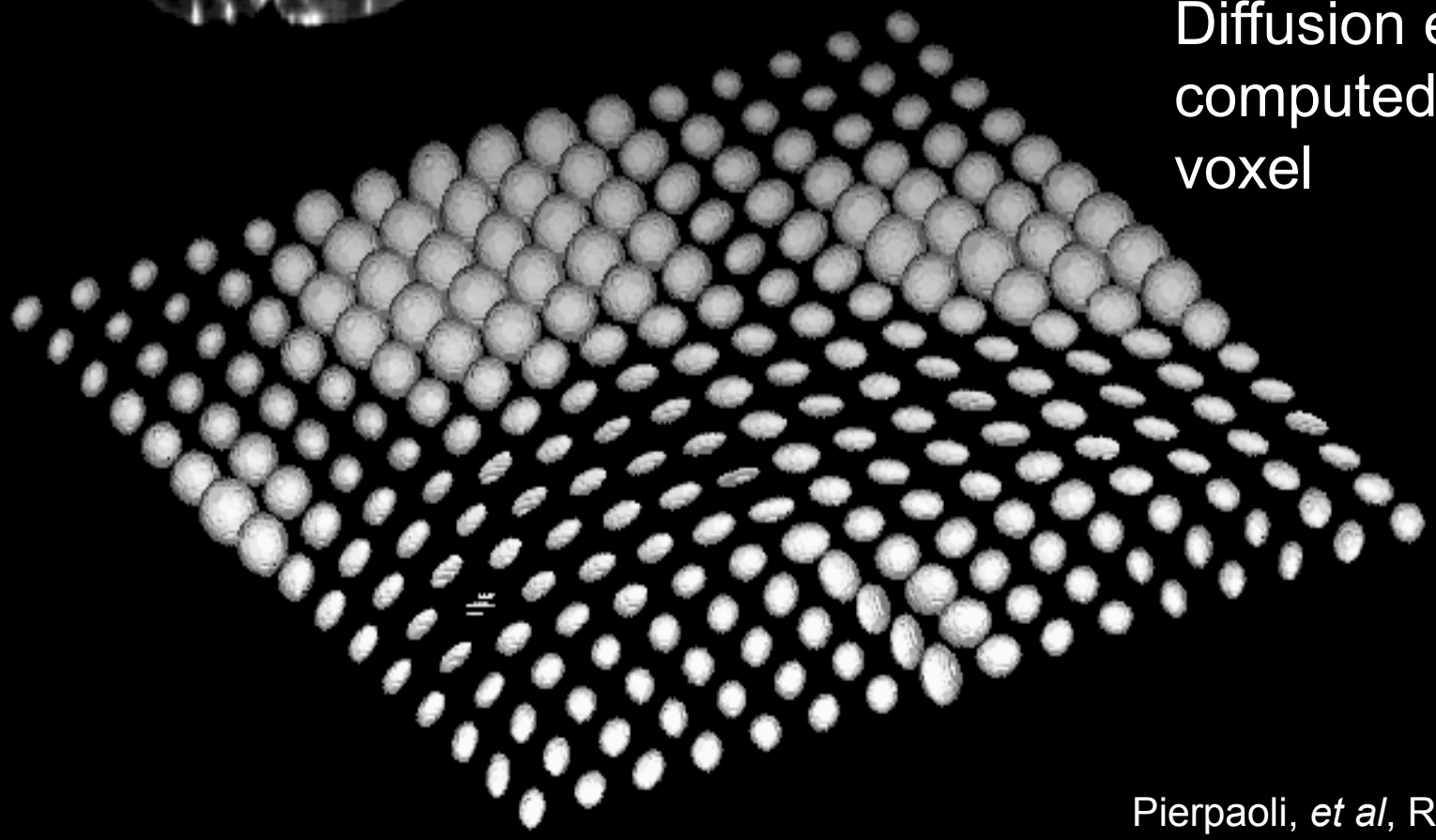






Diffusion Tensor MRI of the Human Brain.

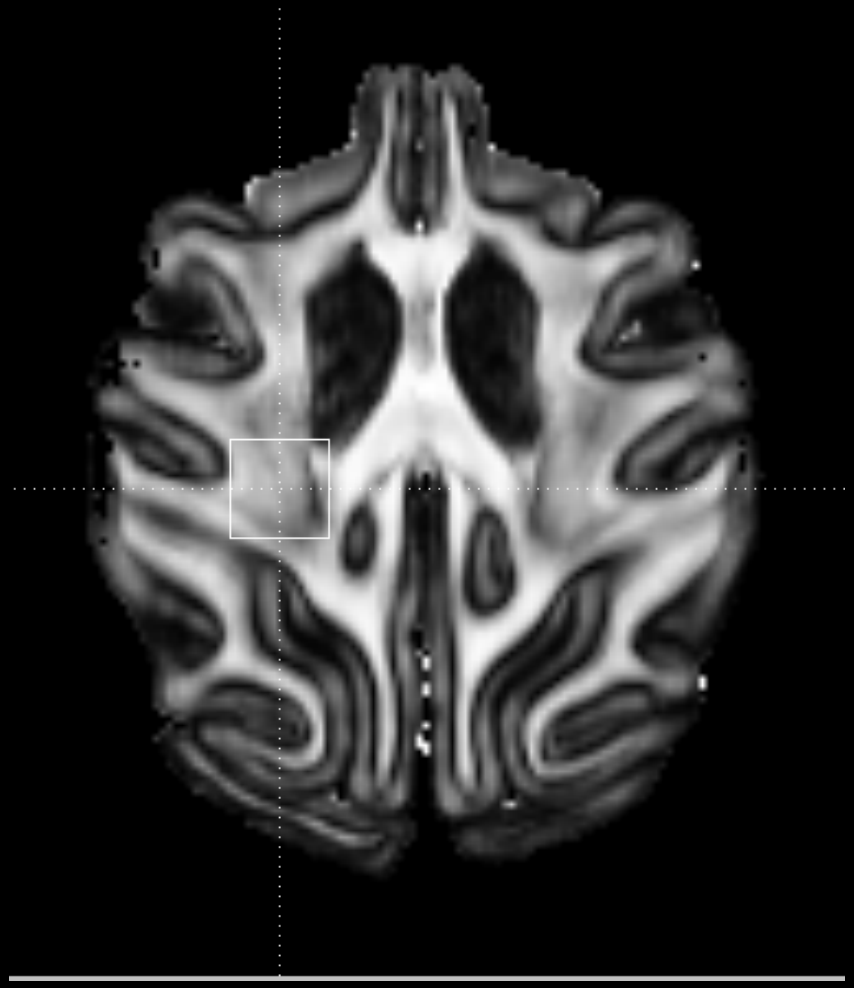


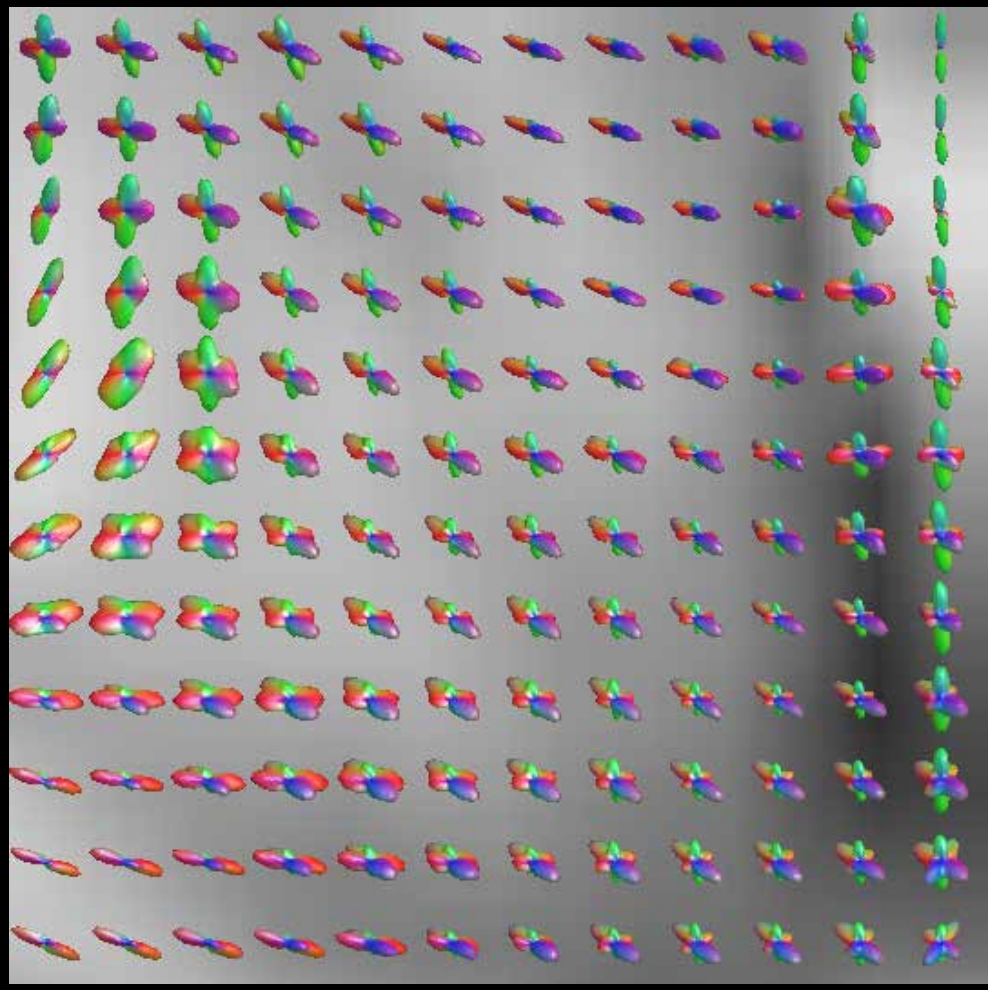


Diffusion ellipsoids computed in each voxel

Pierpaoli, *et al*, Radiology, 1996

HARDI (High Angular Resolution Diffusion Imaging)





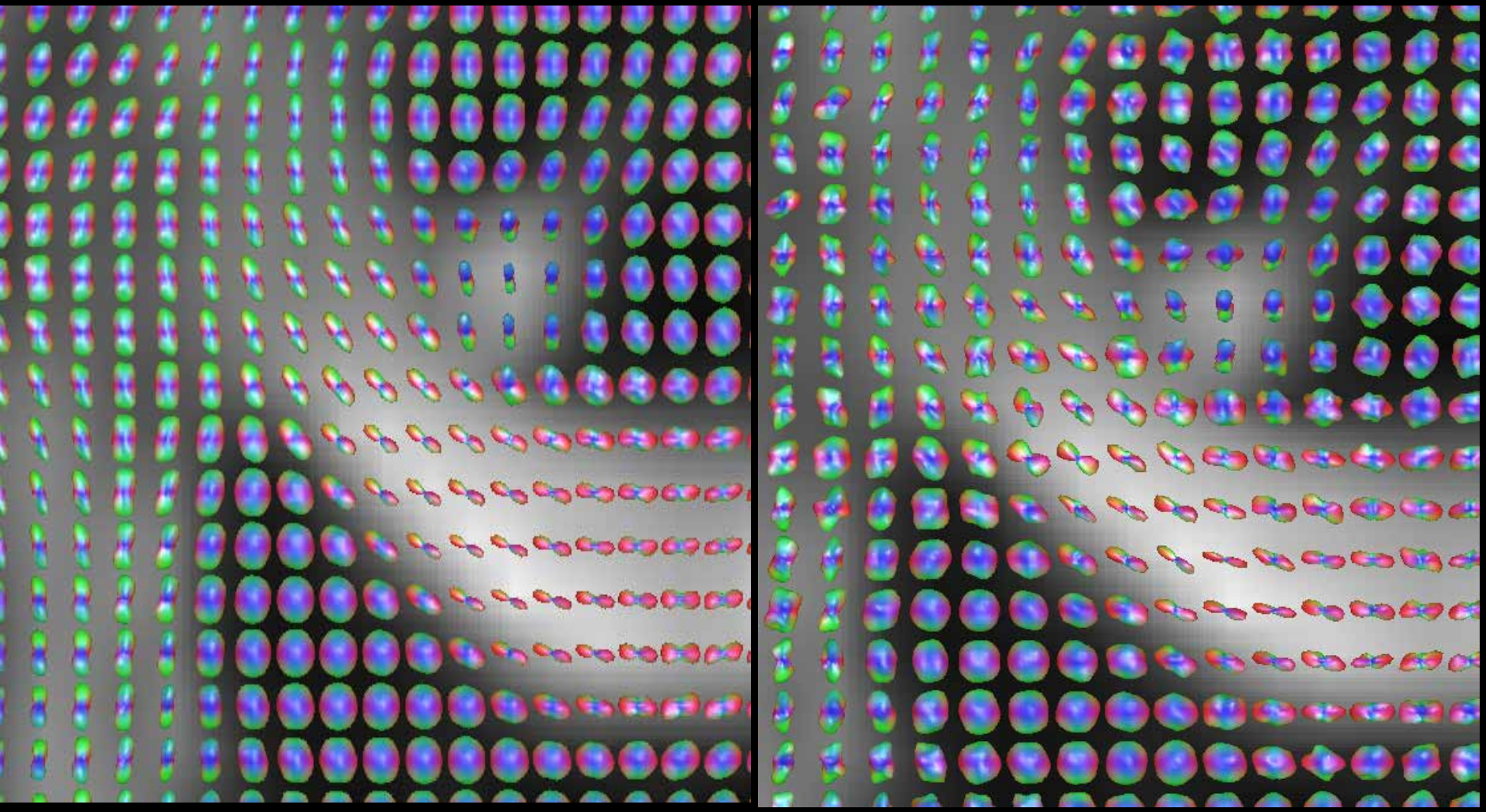
Slide courtesy of Everen Ozarslan (DT-MAP)

Diffusion MRI

Diffusion tensor Imaging: minimum 6 directions, b-value = 800-1200. Spatial resolution: 2x2x2 mm

HARDI (High Angular Resolution Difusion Imaging): minimum 40-60 directions, b-value: 3,000 and higher. Spatial resolution: 3x3x3 mm

HARDI reconstruction, longitudinal data, some subject



A

B

Poll question

What determined the difference between scan A and B:

1) In scan A the subject was younger and the immature brain had less connections

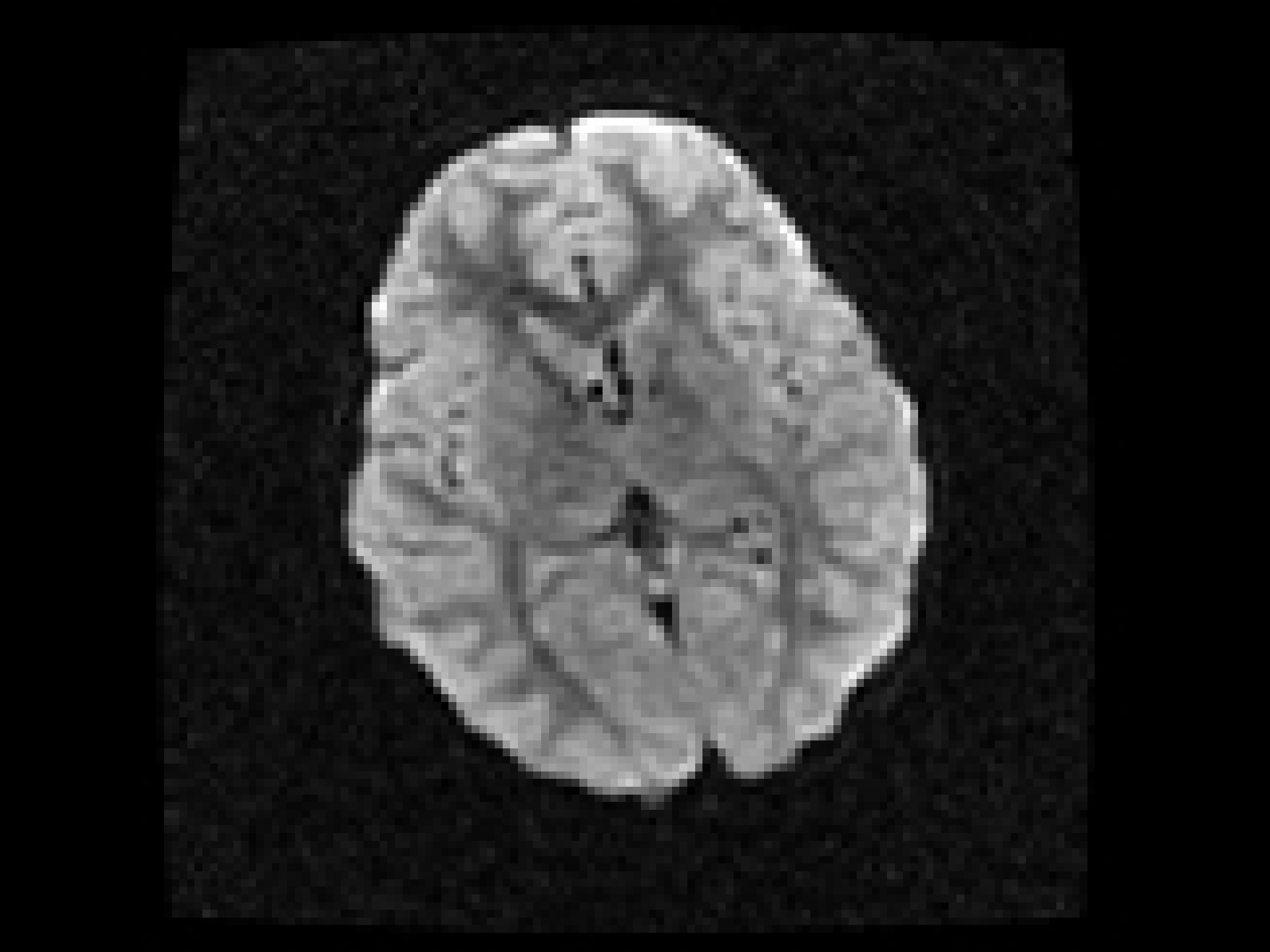
2) Scan A was in the acute phase of trauma, scan B at a later time shows brain reorganization

3) Pattern compatible with all of the above

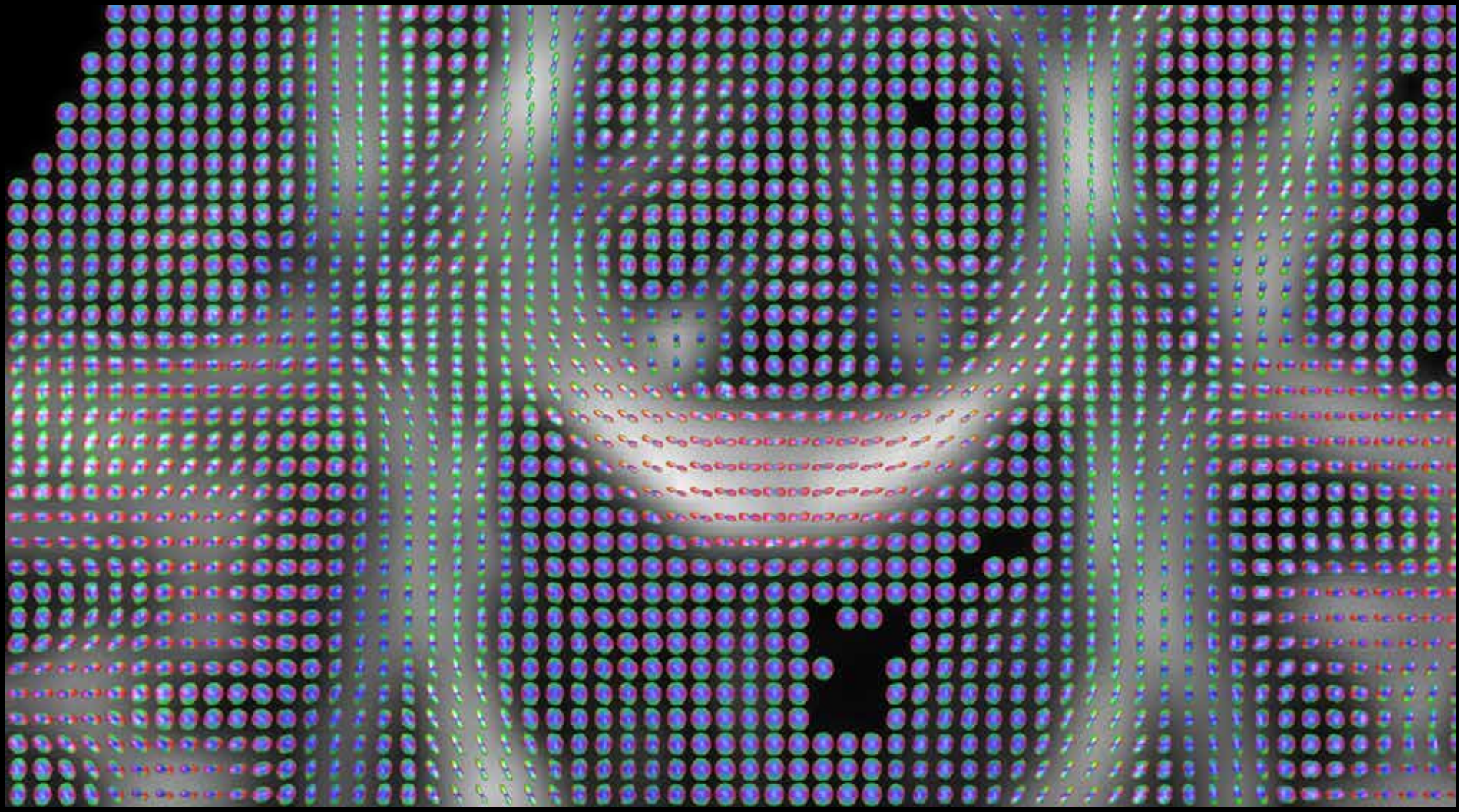
4) Some strange experimental artifact

DTI vs. HARDI

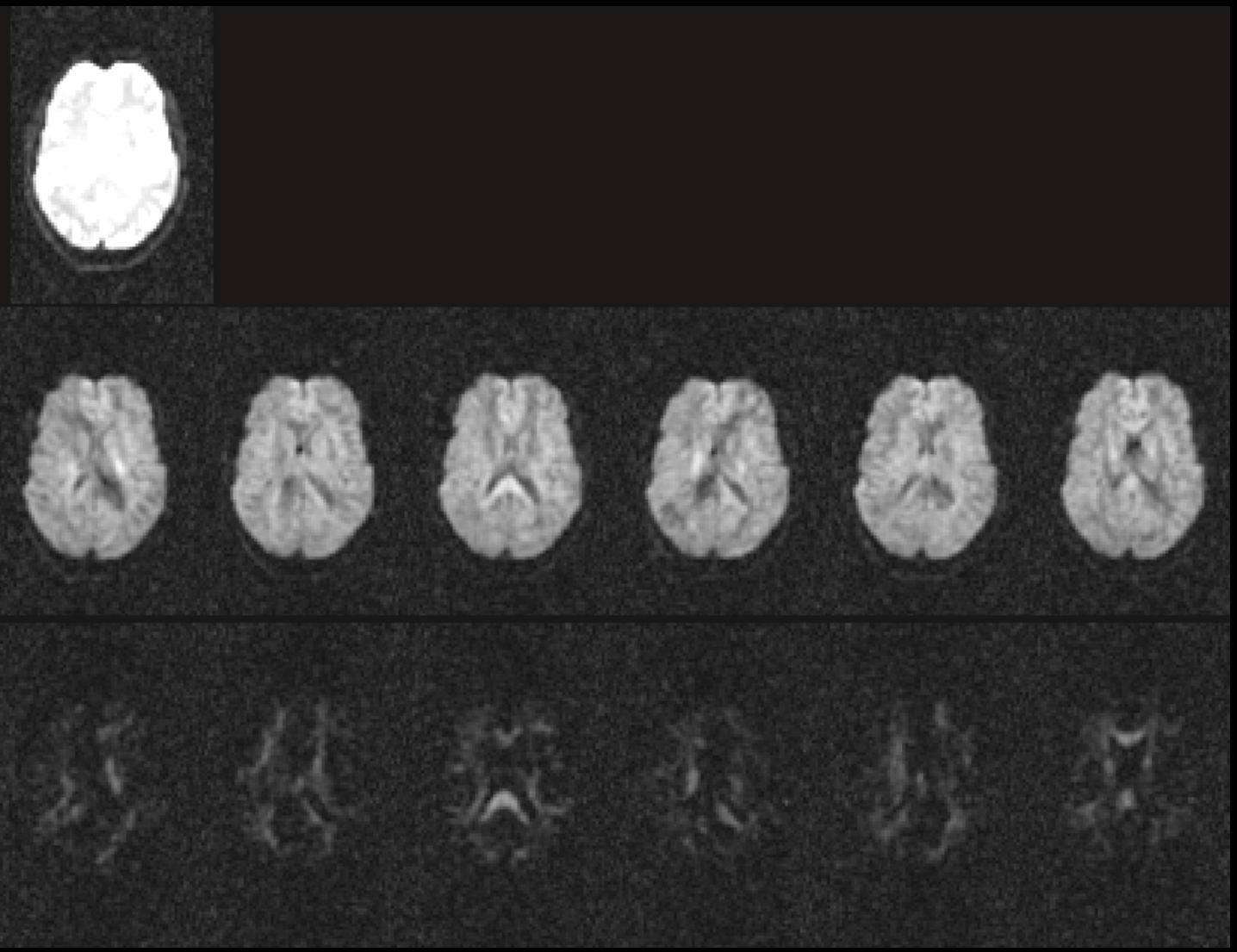
1) Proper HARDI requires a larger amount of high quality data than DTI. In a clinical setting, artifacts can be easily mistaken for biologically meaningful findings



HARDI reconstruction from previous data



Registration of high b-value images. A standing challenge.



B = 30 s/mm^2

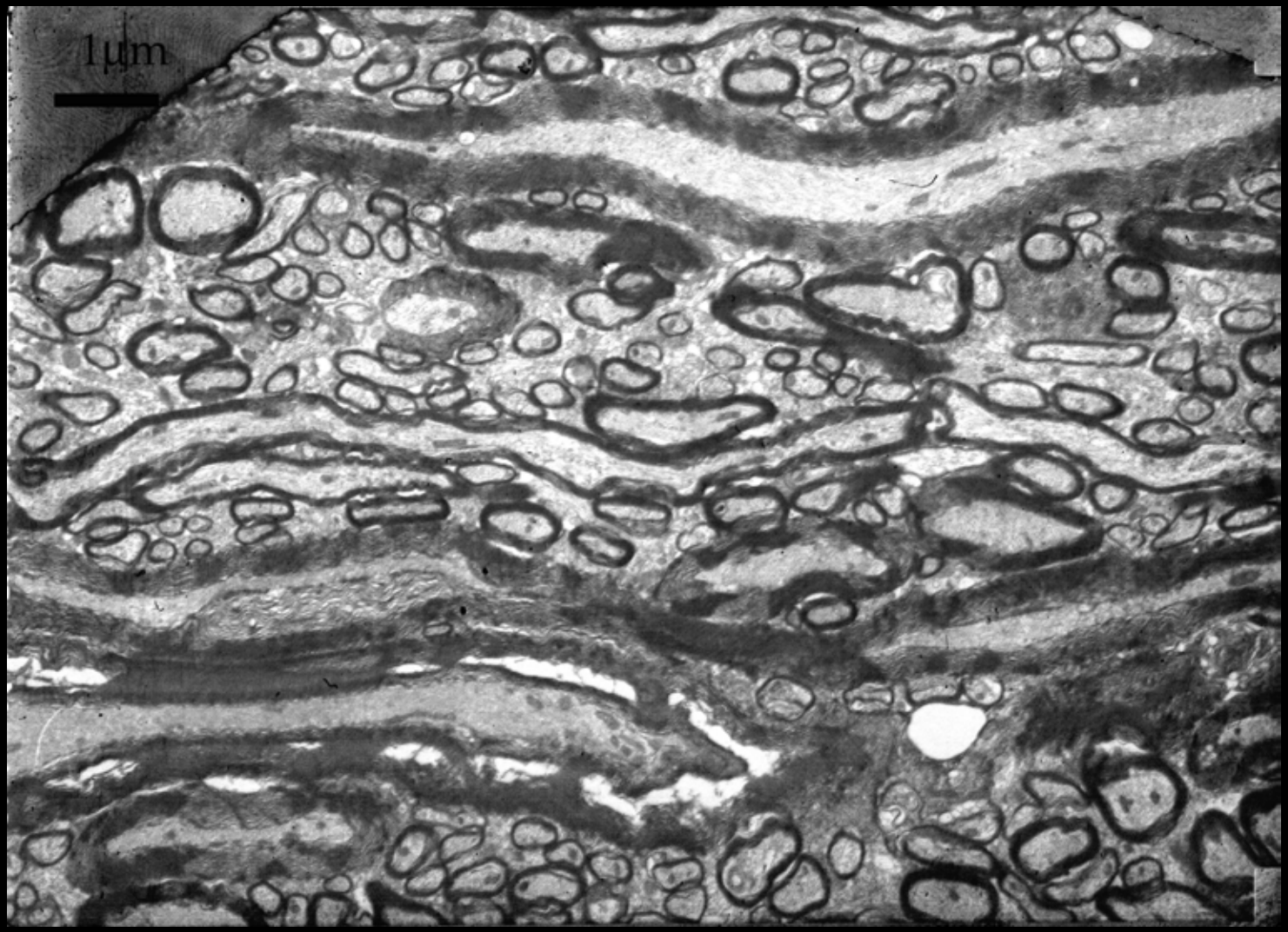
B = 900 s/mm^2

B = 9000 s/mm^2

DTI vs. HARDI

1) Proper HARDI requires a larger amount of high quality data than DTI. In a clinical setting, artifacts can be easily mistaken for biologically meaningful findings

2) HARDI is almost exclusively used for “tractography” and “connettivity”. Diffusion MRI is ill-suited to investigate brain structural connectivity.


1μm

DTI vs. HARDI

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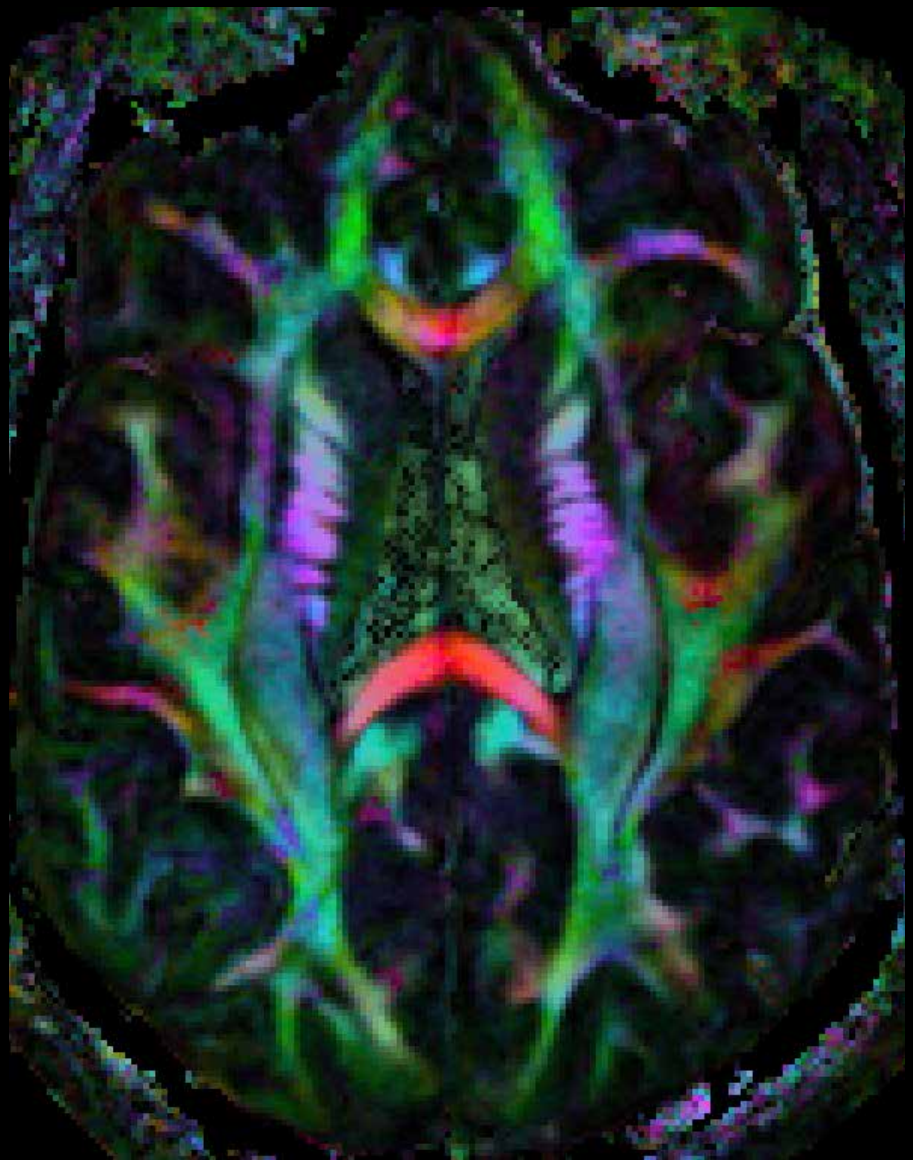
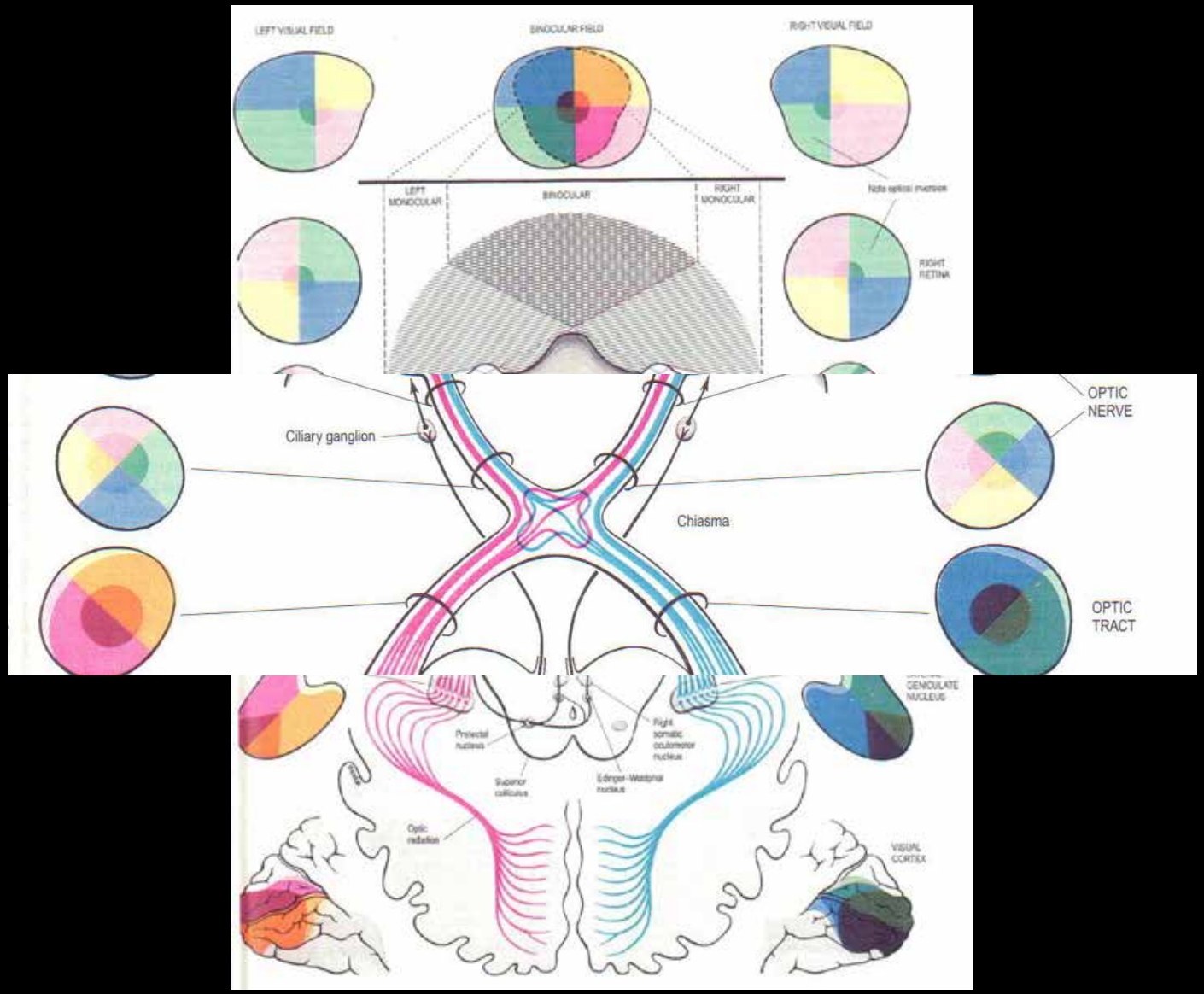
2) HARDI is almost exclusively used for “tractography” and “connettivity”. Diffusion MRI is ill-suited to investigate brain structural connectivity.

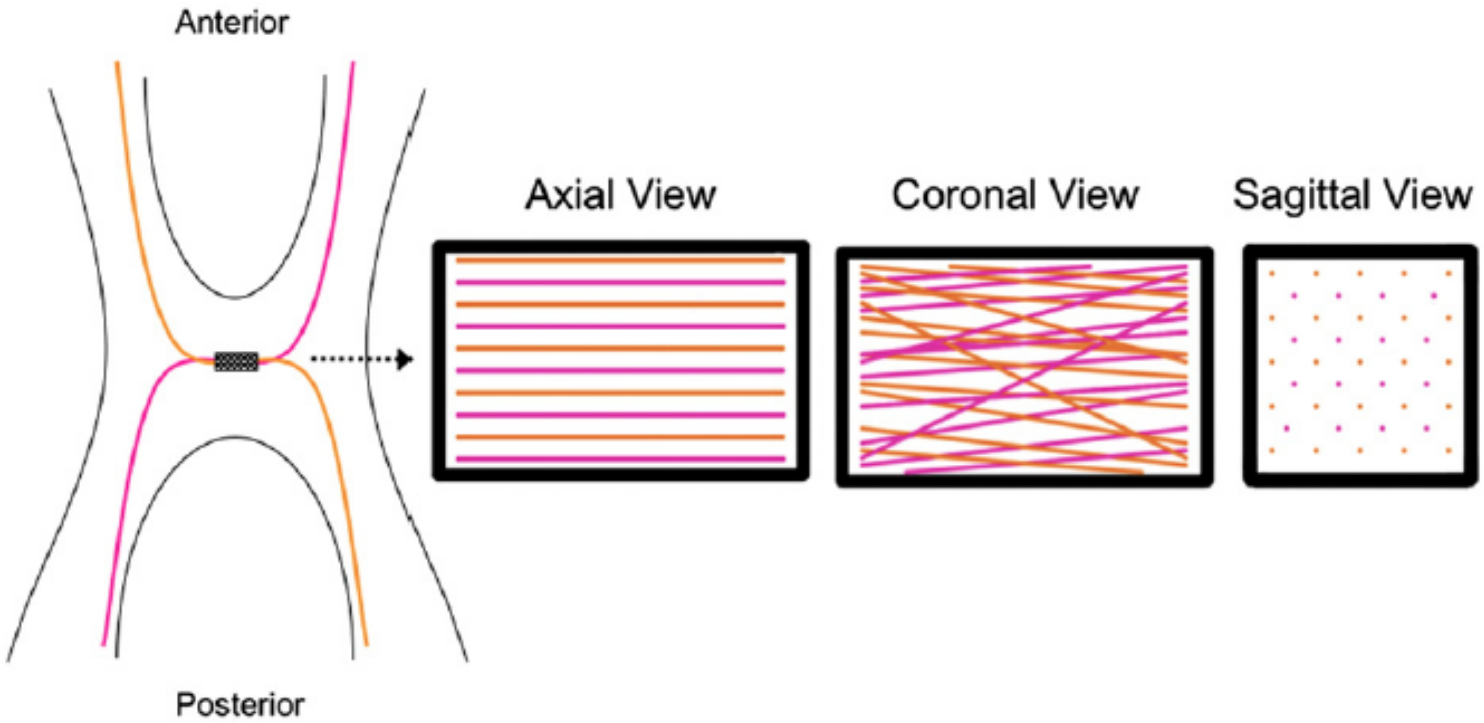
3) There is no free lunch. … with HARDI one has to trade-off resolution to characterize a more complex displacement profile.

Radial Diffusion MRI for sub-millimeter resolution DTI (Sarlls et al. Neuroimage 2009)





Standring, S. (Ed.), 2005. Gray's Anatomy: The Anatomical Basis of Clinical Practise. 39 ed. Elsevier Churchill Livingstone, Edinburgh, London.



of the proposed crossing trajectory pattern in the central chiasm. The pattern is shown from the three orthogonal views: axial, coronal, and sagittal. The co
here is a superior/inferior component to the trajectory consequent of the topological rearrangement of fibers from the optic nerve to optic tract.

DTI vs. HARDI

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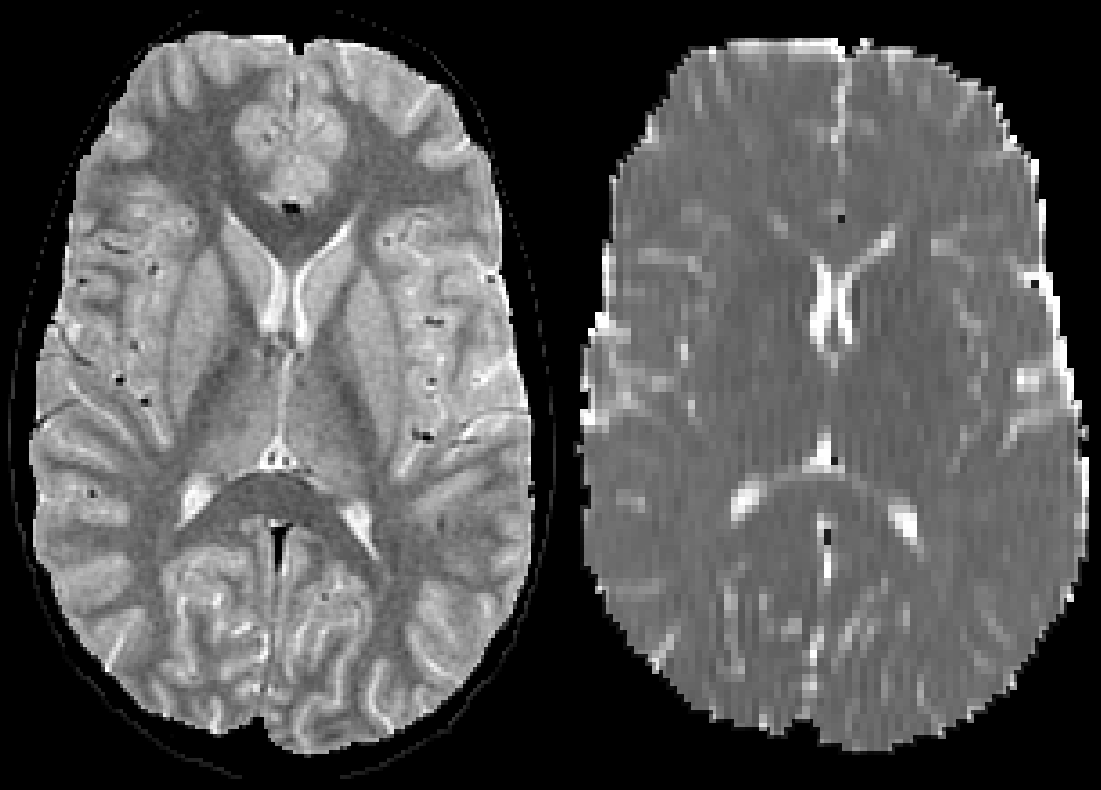
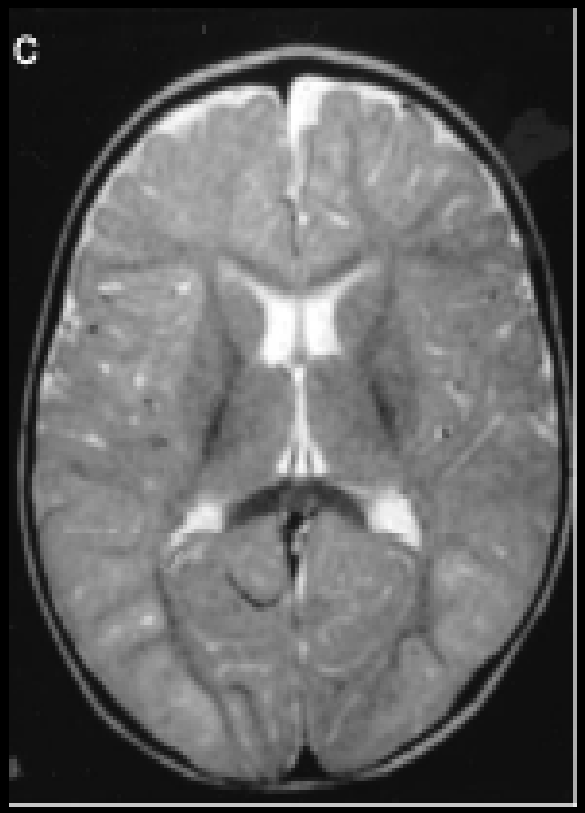
4) Clinical usefulness: DTI ++, HARDI ??

Trace(D) (averaged mean-squared displacement)

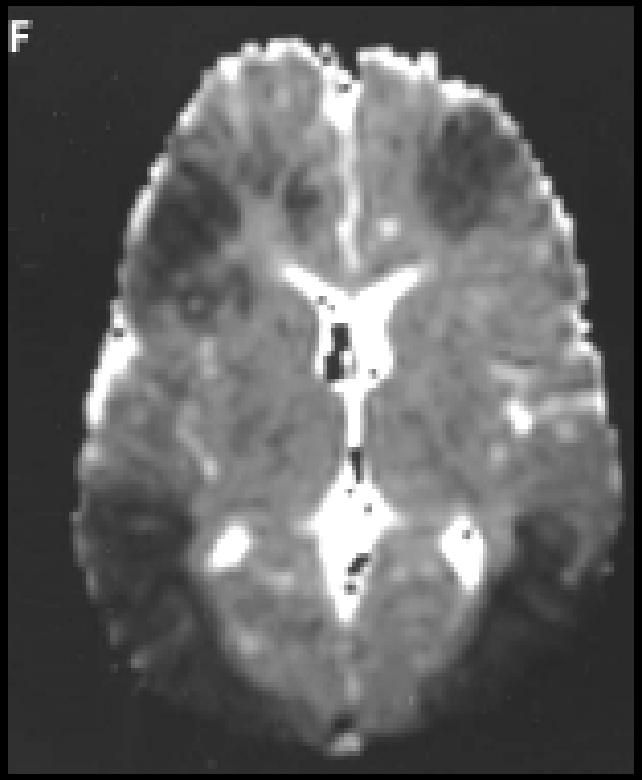


- Trace(**D**) is homogeneous in normal brain parenchyma
- Low inter-subject variability

T2 weighted image Trace(D) map (also called ADC or MD)



T2WI



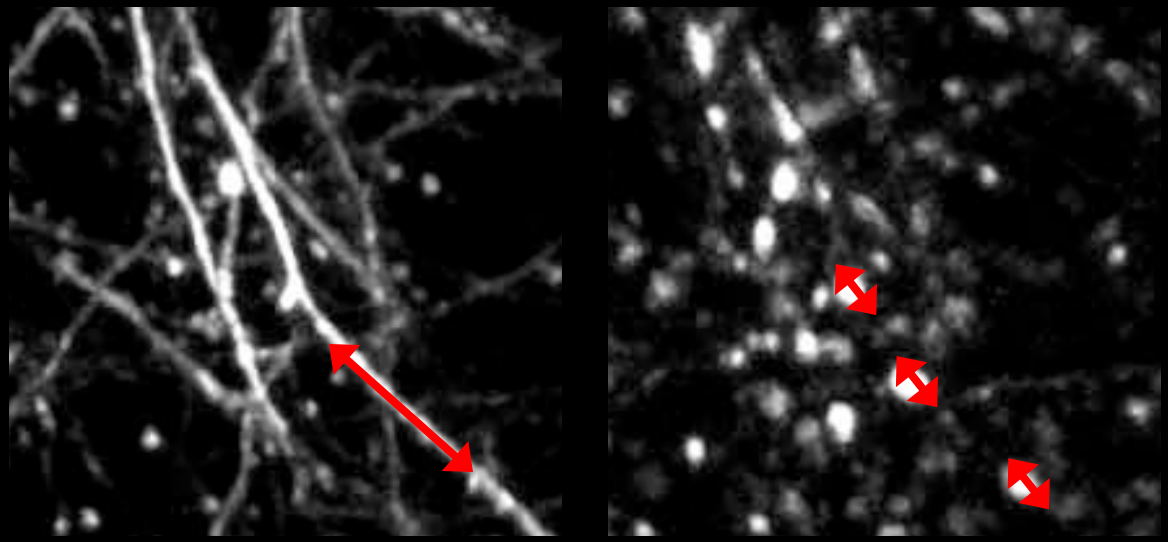
Trace(D)

7.5-month old boy who reportedly fell off the bed onto a carpeted floor. Scan performed 1 day after presentation.

Suh DY et al Neurosurgery, Vol. 49, No. 2, August 2001, 309-20

Hypothesis by Matt Budde, et al., PNAS, 2010

Neurite beading is sufficient to decrease ADC_{intra} by restricting water mobility along each neurite.

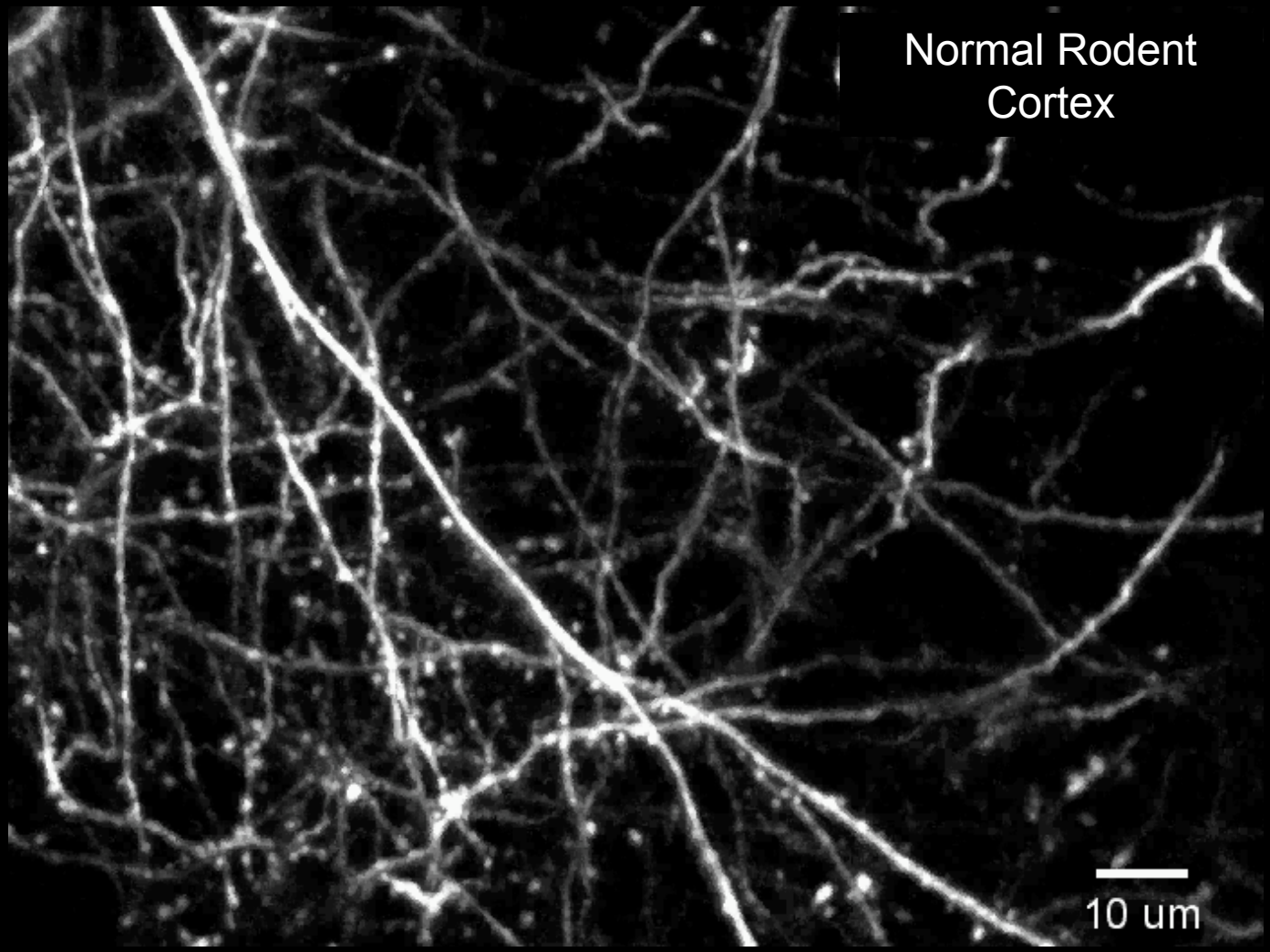


Approach

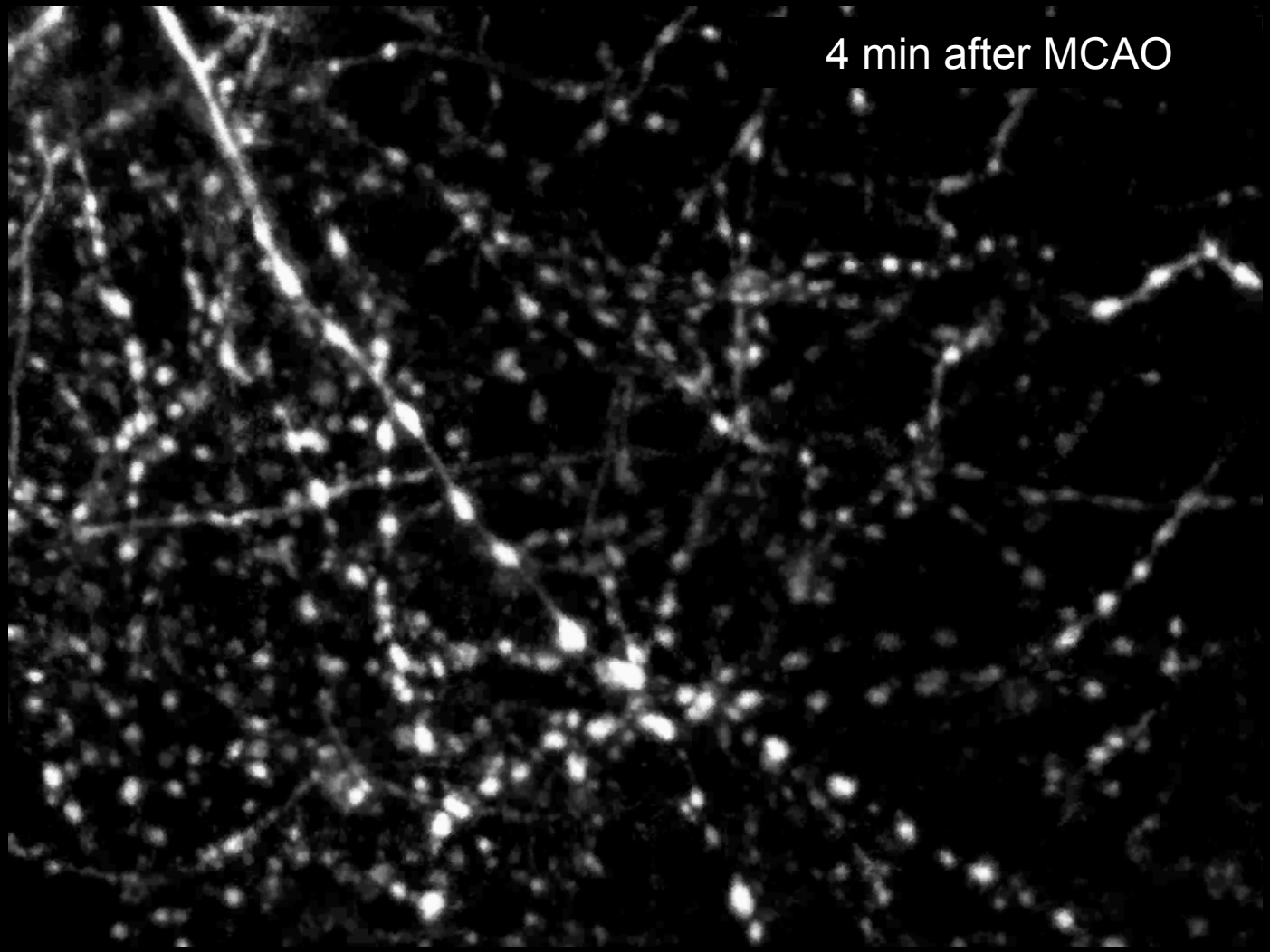
Derive a biophysical model of beading in neurites
Simulate diffusion MR experiment in 3D geometrical surfaces
Validate model in mammalian tissues

What can we learn from other imaging modalities?

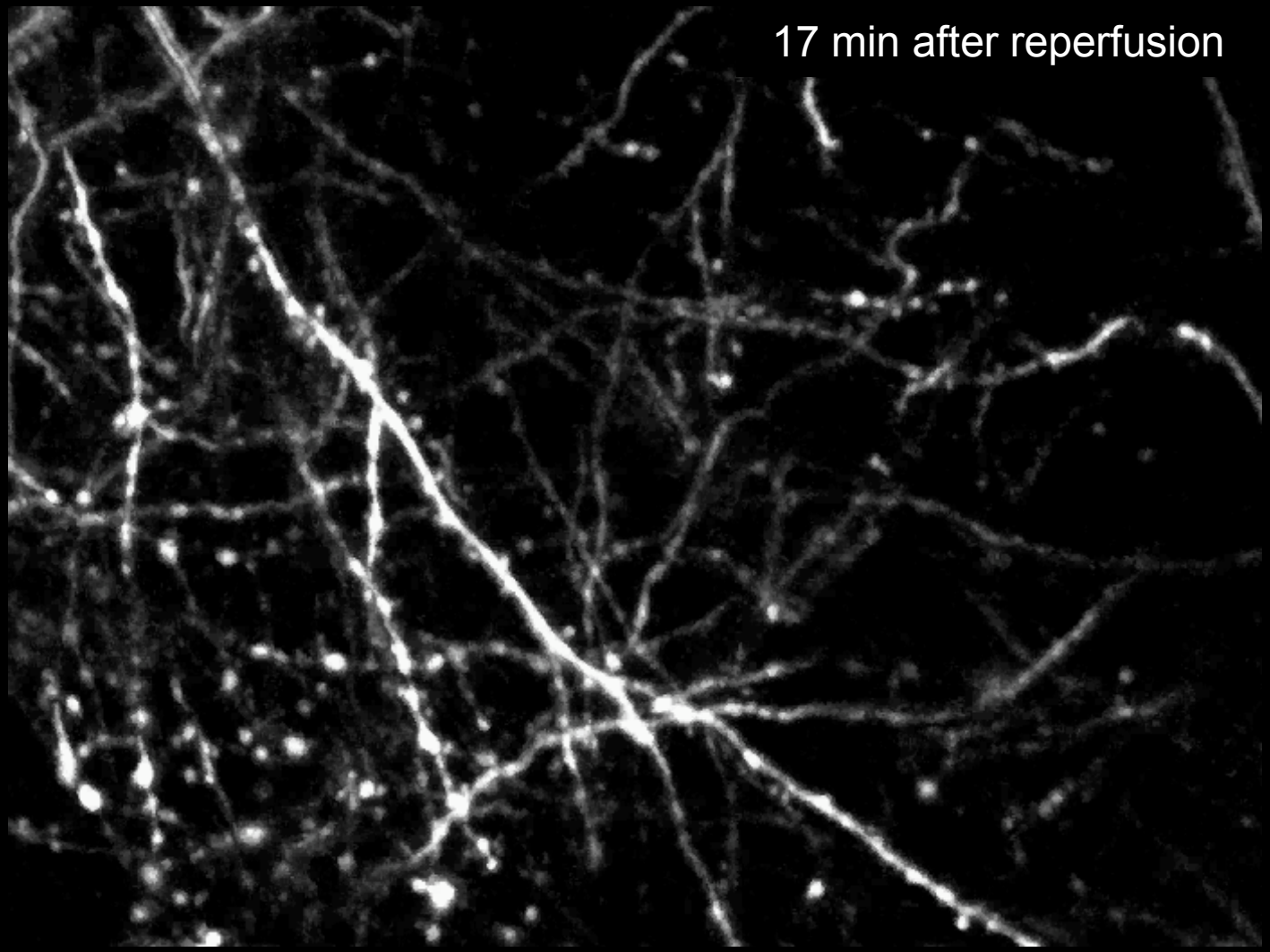
In vivo two-photon microscopy (Murphy T, et al. *J Neurosci* 2008)



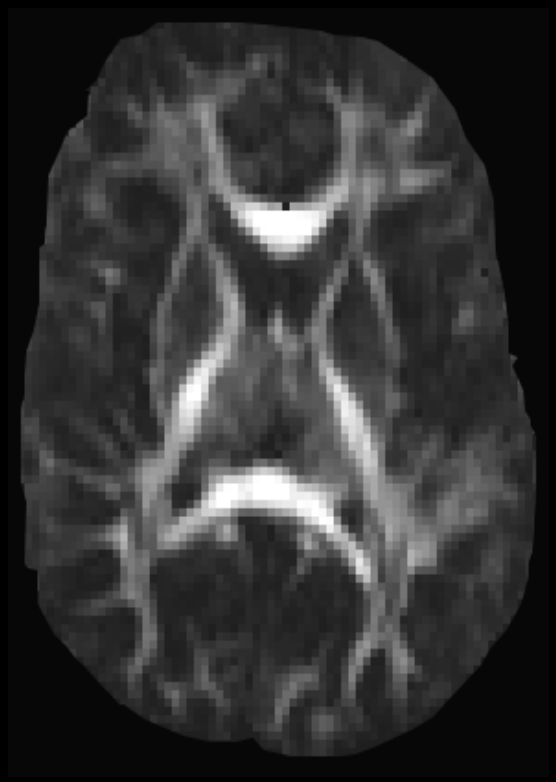
Neurite beading occurs abruptly after ischemia…



…and resolves upon reperfusion.



Diffusion anisotropy (shape of displacement profile)

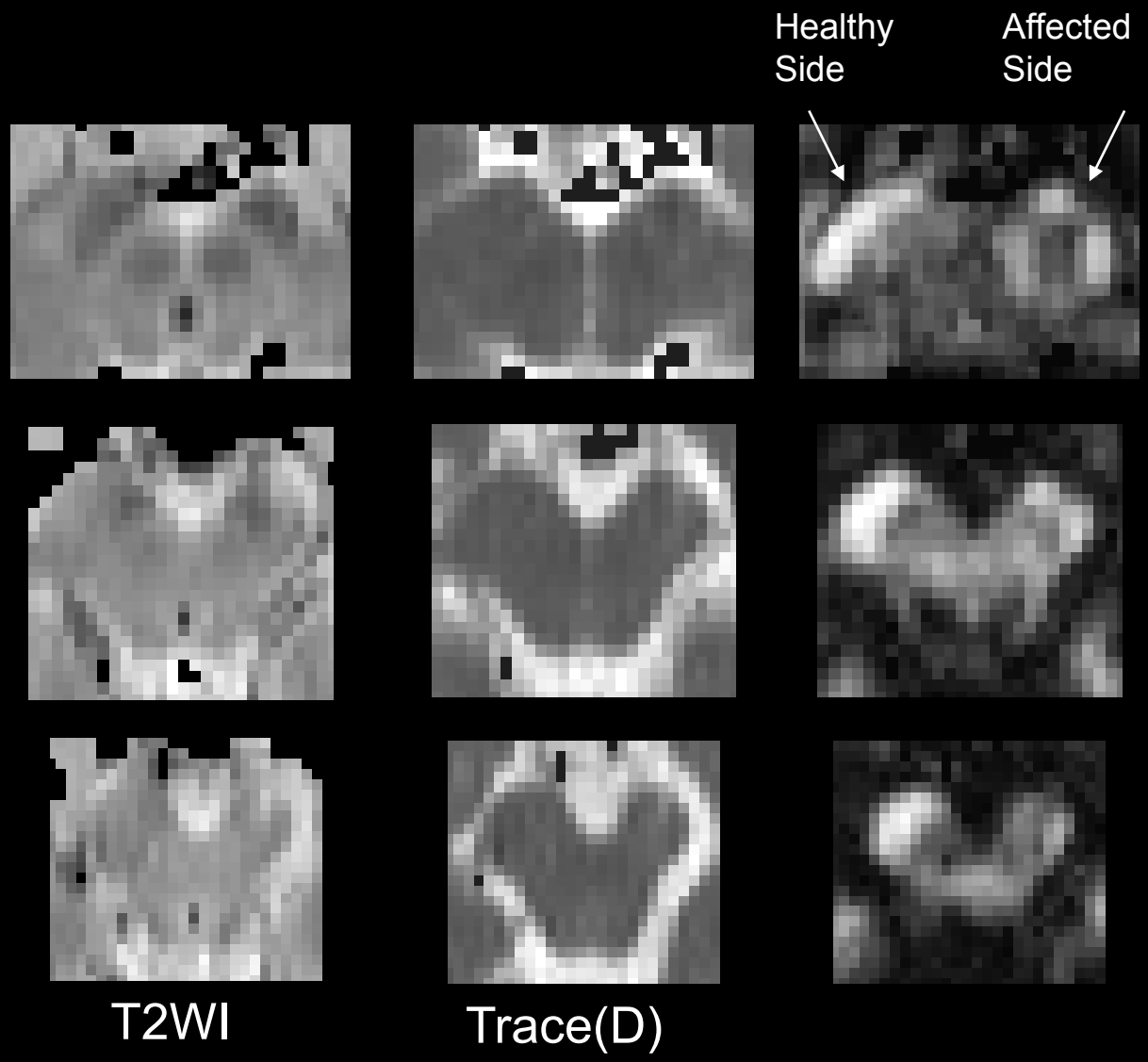


T2 weighted image Anisotropy map

- Diffusion anisotropy is highly variable in normal white matter

- Differences in anisotropy reflect differences in white matter architecture

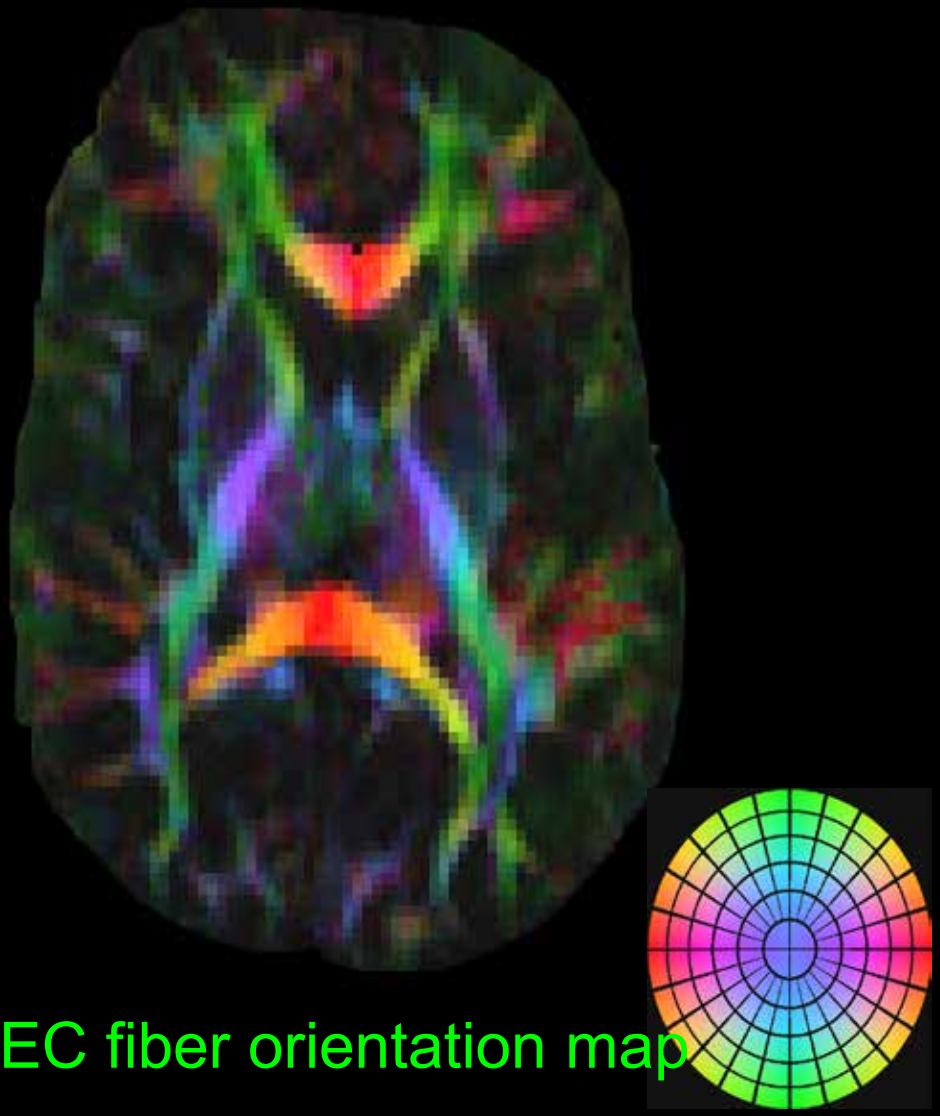
Secondary degeneration in the Cerebral Peduncle



NeuroImage **13,** 1174–1185 (2001)

Fiber orientation

T2 weighted image



DEC fiber orientation map

Pajevic, Pierpaoli, MRM 1999

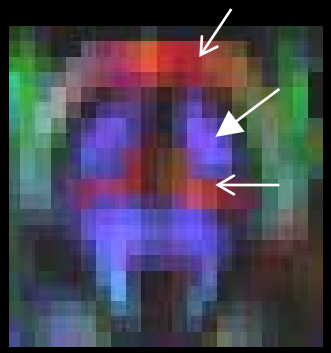
Degeneration of pontocerebellar pathways in Multiple System Atrophy

Transverse Pontine Fibers

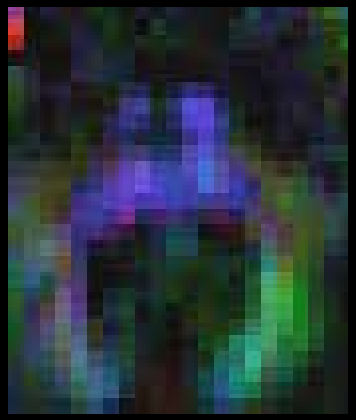
Pyramidal Tract

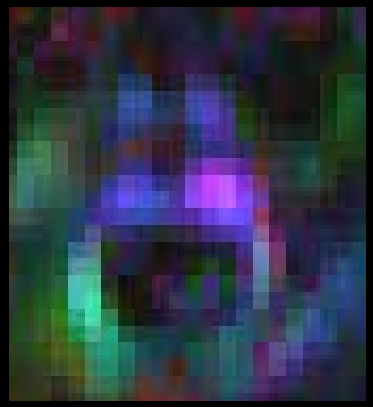
Transverse Pontine Fibers

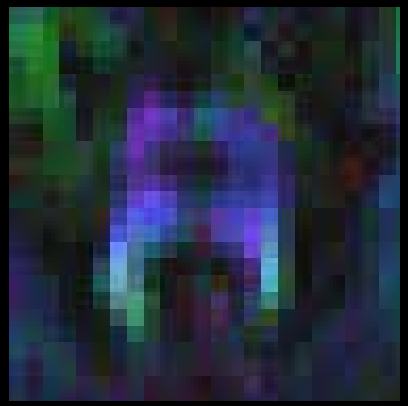
Healthy subject



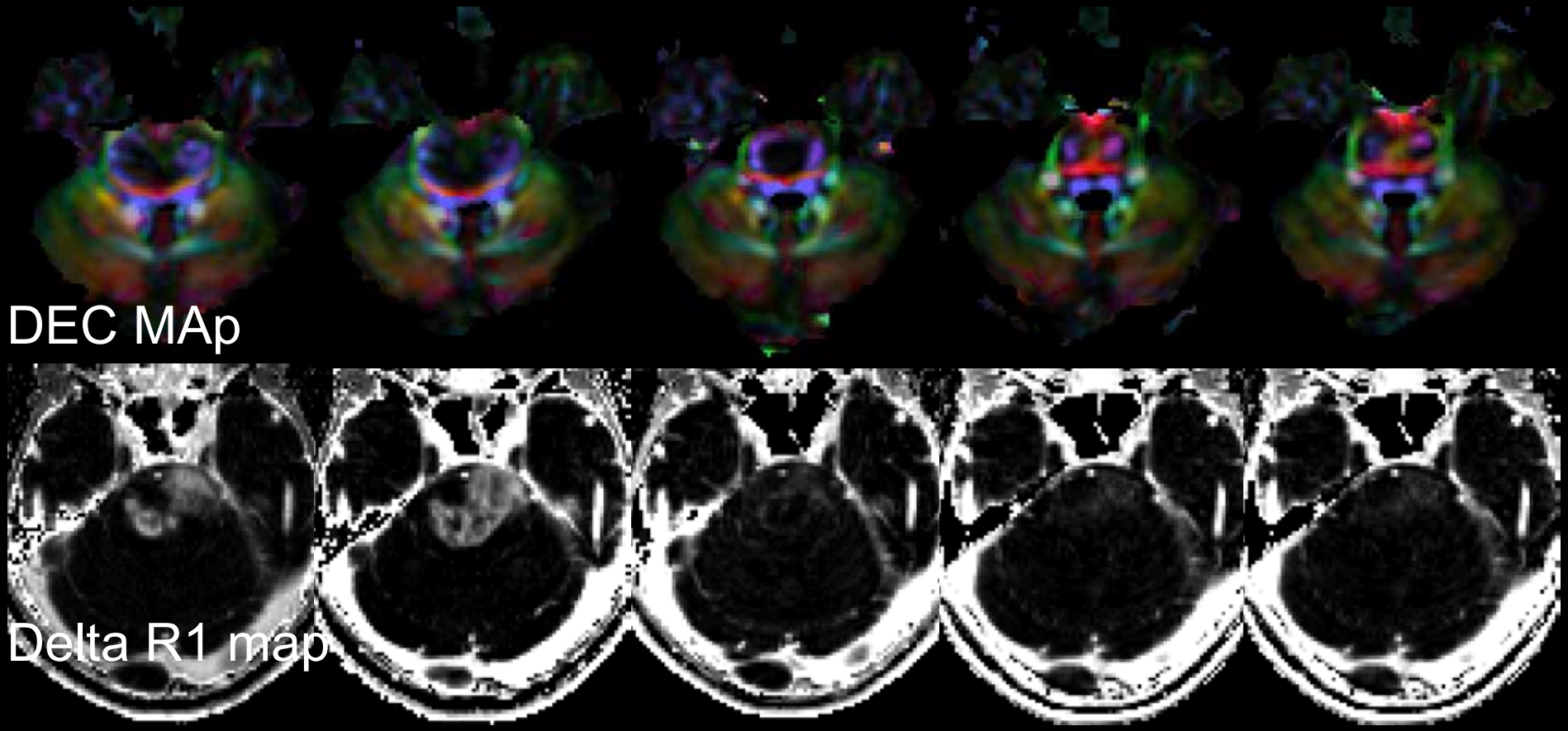
MSA patient







Temporal evolution of a Pontine Glioma



Time 0	Time 1	Time 2	Time 3	Time 4
	T0 + 34 days	T0 + 140 days	T0 + 363 days	T0 + 426 days

CONCLUSIONS

1) Proper HARDI requires a larger amount of of high quality data than DTI. In a clinical setting, artifacts can be easily mistaken for biologically meaningful findings

2) HARDI is almost exclusively used for “tractography” and “connettivity”. Diffusion MRI is ill-suited to investigate brain structural connectivity.

3) There is no free lunch. … with HARDI one has to trade-off resolution to characterize a more complex displacement profile.

4) Clinical usefulness: DTI ++, HARDI ??

NeuroImage 61 (2012) 275–288

Contents lists available at SciVerse ScienceDirect

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journal homepage: www.elsevier.com/locate/ynimg

Effects of image distortions originating from susceptibility variations and concomitant fields on diffusion MRI tractography results

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[d] Section on Clinical Studies, National Institute of Mental Health, National Institute of Health, Bethesda, MD, 20892, USA

FULL PAPER

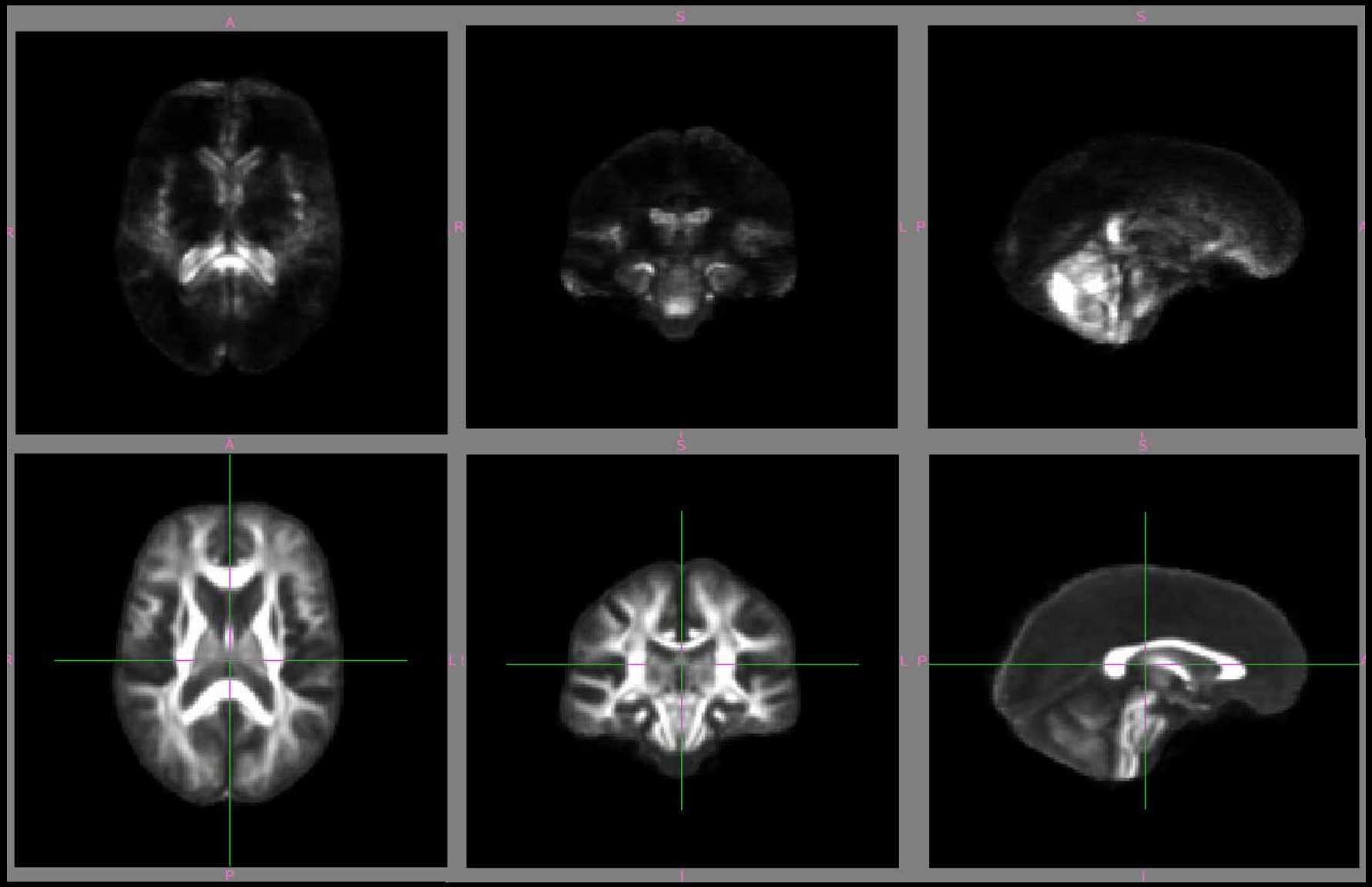
Magnetic Resonance in Medicine 000:000–000 (2012)

Informed RESTORE: A Method for Robust Estimation of Diffusion Tensor from Low Redundancy Datasets in the Presence of Physiological Noise Artifacts

Lin-Ching Chang,[1]* Lindsay Walker,[2,3] and Carlo Pierpaoli[3]

Outlier Rejection Probability Map

Lindsay Walker et al Neuroimage 2011



Diffusion Tensor Imaging in Young Children with Autism: Biological Effects and Potential Confounds

Lindsay Walker, Marta Gozzi, Rhoshel Lenroot, Audrey Thurm, Babak Behseta, Susan Swedo, and Carlo Pierpaoli

Background: Diffusion tensor imaging (DTI) has been used over the past decade to study structural differences in the brains of children with autism compared with typically developing children. These studies generally find reduced fractional anisotropy (FA) and increased mean diffusivity (MD) in children with autism; however, the regional pattern of findings varies greatly.

Methods: We used DTI to investigate the brains of sedated children with autism ($n = 39$) and naturally asleep typically developing children ($n = 39$) between 2 and 8 years of age. Tract based spatial statistics and whole brain voxel-wise analysis were performed to investigate the regional distribution of differences between groups.

Results: In children with autism, we found significantly reduced FA in widespread regions and increased MD only in posterior brain regions. Significant age × group interaction was found, indicating a difference in developmental trends of FA and MD between children with autism and typically developing children. The magnitude of the measured differences between groups was small, on the order of approximately 1%–2%. Subjects and control subjects showed distinct regional differences in imaging artifacts that can affect DTI measures.

Conclusions: We found statistically significant differences in DTI metrics between children with autism and typically developing children, including different developmental trends of these metrics. However, this study indicates that between-group differences in DTI studies of autism should be interpreted with caution, because their small magnitude make these measurements particularly vulnerable to the effects of artifacts and confounds, which might lead to false positive and/or false negative biological inferences.

Biological Psychiatry, 2013

Mid-Atlantic
MIRECC
Mental Illness Research, Education & Clinical Center

White Matter Damage in Blast-exposed Veterans without Mild TBI

Rajendra Morey, M.D.

Associate Professor

Background

- Exposure to explosive forces from bombs is common in Veterans of recent military conflicts
- Majority of traumatic brain injury (TBI) at forward deployed medical facilities involves exposure an improvised explosive device (IED), grenade, rocket-propelled grenade (RPG), or mortar fire.
- Damage to brain tissue (white matter) using Diffusion Tensor Imaging (DTI) is well established in cases that clinical symptoms of mild TBI.
- Recent studies of sports participants show compromised white matter integrity even in the absence of clear concussive symptoms.

RESEARCH LETTER

White Matter Integrity in the Brains of Professional Soccer Players Without a Symptomatic Concussion

To the Editor: Soccer is the most popular sport in the world, with more than 250 million active players.[1] It is the only sport in which the unprotected head is a primary point of contact when heading the ball. In other contact sports, the deleterious long-term effects of repetitive traumatic brain

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Neurosurg Focus 33 (6):E3, 2012

A prospective study of physician-observed concussion during a varsity university hockey season: white matter integrity in ice hockey players. Part 3 of 4

*Inga K. Koerte, M.D.,[1,3] David Kaufmann, M.D.,[1,3] Elisabeth Hartl, M.D.,[1] Sylvain Bouix, Ph.D.,[1] Ofer Pasternak, Ph.D.,[1] Marek Kubicki, M.D., Ph.D.,[1,2] Alexander Rauscher, Ph.D.,[4] David K. B. Li, M.D.,[4] Shiroy B. Dadachanji, M.D.,[5] Jack A. Taunton, M.Sc., M.D.,[5] Lorie A. Forwell, M.Sc.P.T.,[6] Andrew M. Johnson, Ph.D.,[7] Paul S. Echlin, M.D.,[8] and Martha E. Shenton, Ph.D.[1,2,9]

Object. The aim of this study was to investigate the effect of repetitive head impacts on white matter integrity that were sustained during 1 Canadian Interuniversity Sports (CIS) ice hockey season, using advanced diffusion tensor imaging (DTI).

Methods. Twenty-five male ice hockey players between 20 and 26 years of age (mean age 22.24 ± 1.59 years) participated in this study. Participants underwent pre- and postseason 3-T MRI, including DTI. Group analyses were performed using paired-group tract-based spatial statistics to test for differences between preseason and postseason changes.

Results. Tract-based spatial statistics revealed an increase in trace, radial diffusivity (RD), and axial diffusivity (AD) over the course of 1 season. Compared with preseason data, postseason images showed higher trace, AD, and RD values in the right precentral region, the right corona radiata, and the anterior and posterior limb of the internal capsule. These regions involve parts of the corticospinal tract, the corpus callosum, and the superior longitudinal fasciculus. No significant differences were observed between preseason and postseason for fractional anisotropy.

Conclusions. Diffusion tensor imaging revealed changes in white matter diffusivity in male ice hockey players over the course of 1 season. The origin of these findings needs to be elucidated.

Poll question #1

- How many of you are familiar with the Junior Seau case?
  - Yes
  - No
  - Not sure

55

Poll Question #2

Is there prominent injury to brain tissue in Veterans with blast exposure <u>without</u> clinical symptoms of TBI ?

- Yes
- No
- Not sure

Subconcussive blast exposure

- 6 Veterans with pure primary blast mTBI
- 16 blast exposed without mTBI
- 23 blast unexposed
- All had DTI scans in the chronic stage

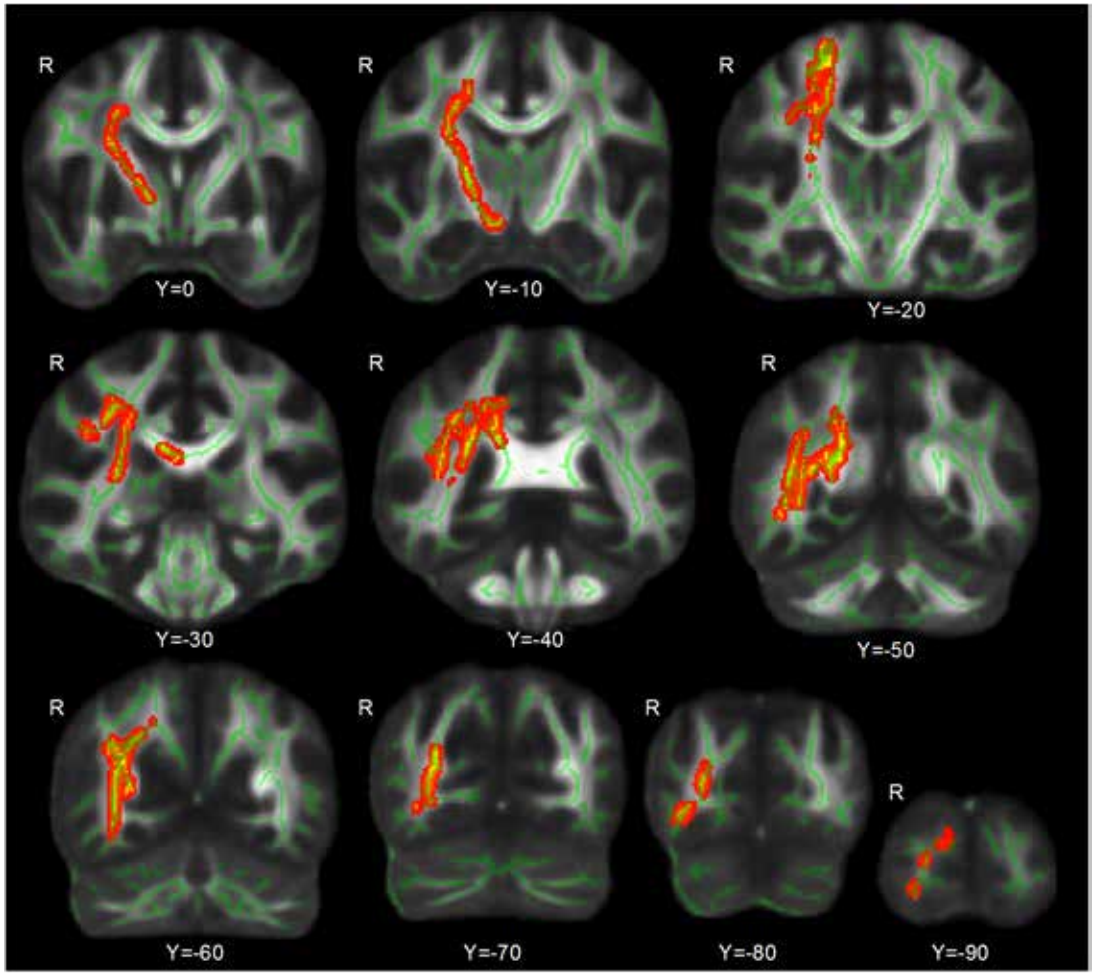


Figure1. Whole brain voxelwise comparison of FA between the blast-exposed and the blast-unexposed control group was covaried for age and severity of PTSD (CAPS score). These results show significantly lower FA in the blast-exposed group compared to the blast-unexposed group in diffuse cortical and subcortical tracts based in the right hemisphere including the forceps major, superior and inferior longitudinal fasciculus, anterior thalamic radiations, inferior fronto-occipital fasciculus, and the corticospinal tract ($p < .05$; corrected).

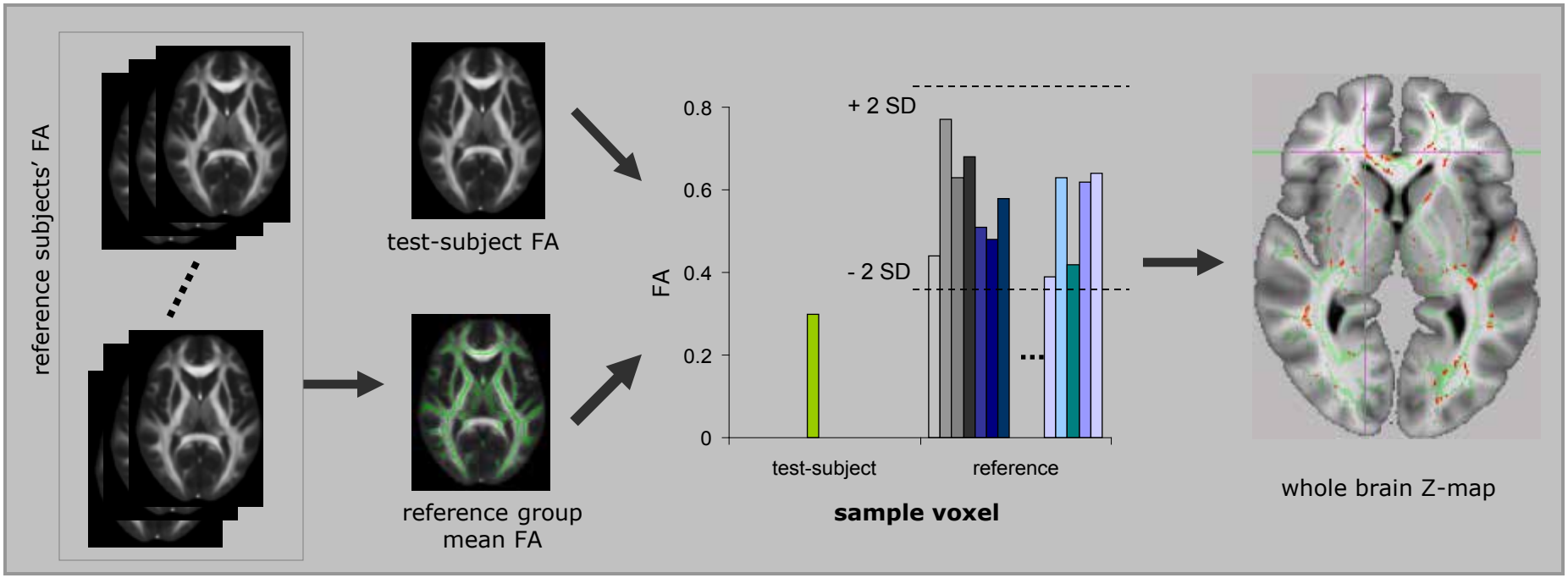


Figure 1. Following preprocessing of DTI data, the analytic approach was based on registration of FA maps as implemented in the FSL tract based spatial statistics (TBSS). The primary statistical approach used the standard deviation of fractional anisotropy for each voxel in the reference group. Using the mean and standard deviation of FA for the reference group, the test-subject's voxels were compared to the skeleton voxels (green highlight) that were generated for the reference group. For the test-subject, we computed a statistical map that reflects the number of standard deviations below the mean of the reference group, which is effectively a z- map. The whole brain z-map shows voxels (in red) where FA of the test-subject was found to be greater than two standard deviations below the mean FA of the reference group.

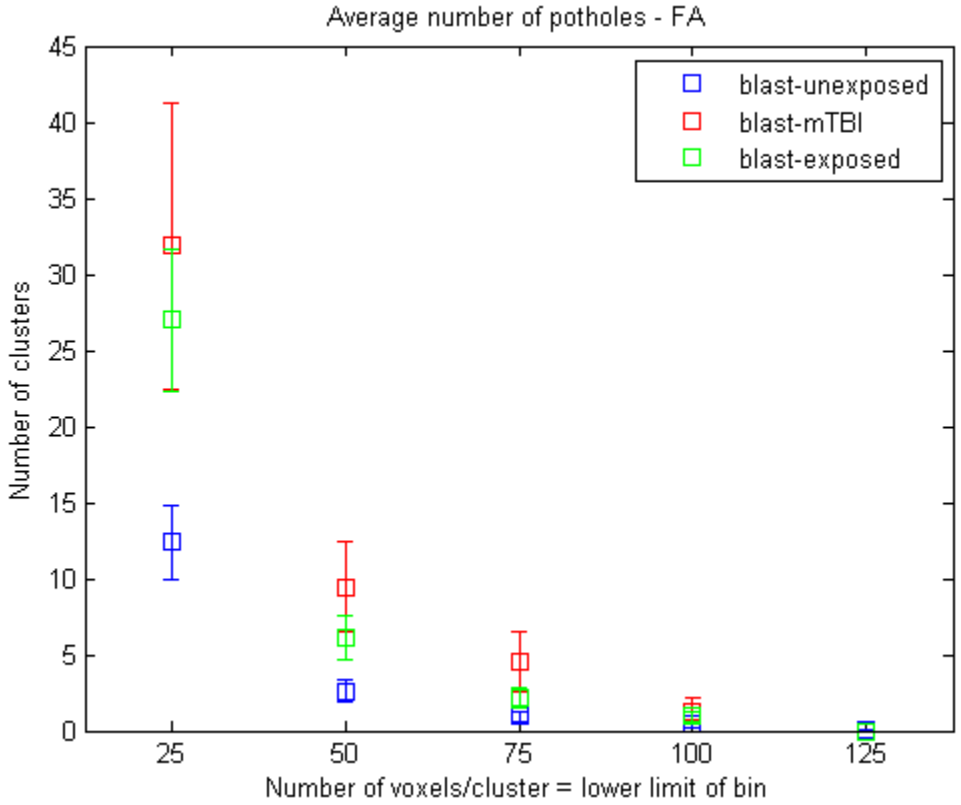
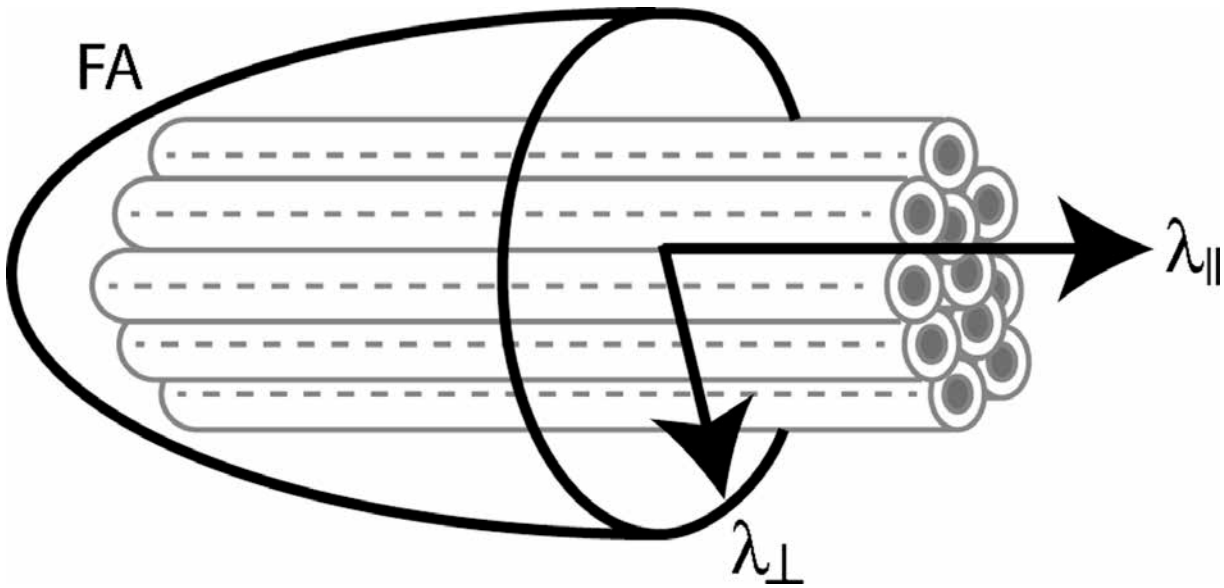


Figure 2. There was a significant main effect of group [F(2,42)=4.4, *p*=.02] on the number of small (25-50 voxel), medium (50-75 voxel), and large (75-100 voxel) potholes, which were defined by low FA values ($z < -2$). The blast-unexposed control group had significantly fewer potholes than the blast-mTBI group ($p = .009$) and the blast-exposed group ($p = .036$). Based on the number of potholes, the blast-exposed group resembled the blast-mTBI group when considered in relation to the blast-unexposed control group

Radial and Axial Diffusivity



$$FA = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}}{\sqrt{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

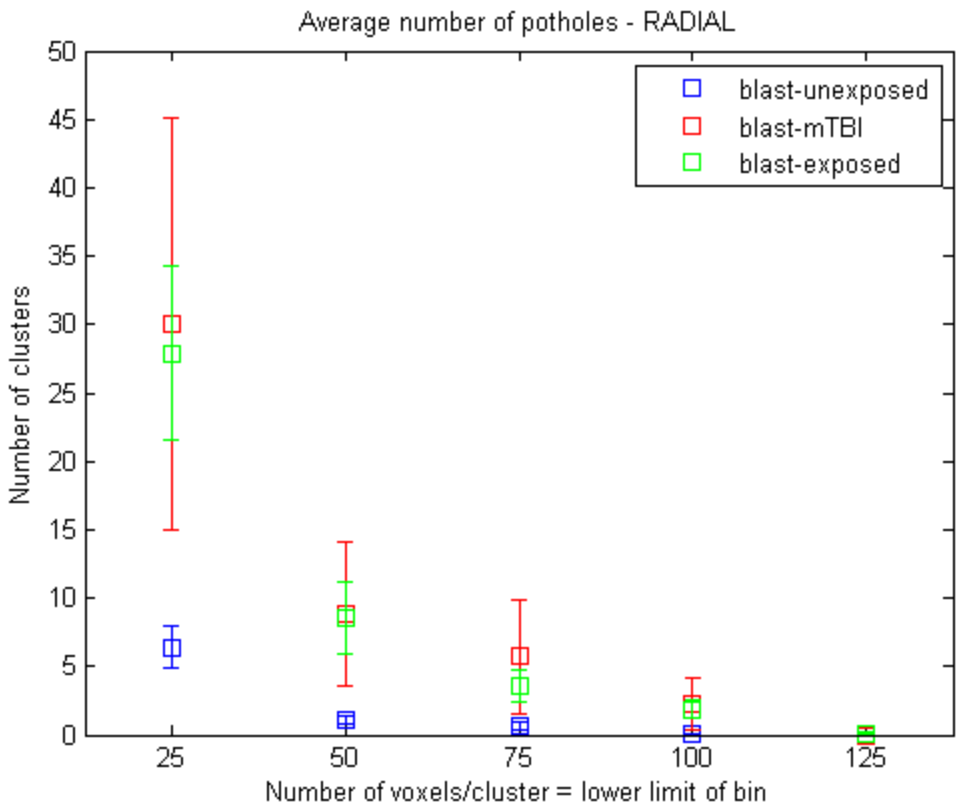


Figure 4. There was a significant main effect of group [F(2,42)=3.7, *p*=.034] on the number of small (25-50 voxel), medium (50-75 voxel), and large (75-100 voxel) potholes, which were defined by low radial diffusivity (z < -2). The blast-unexposed control group had significantly fewer radial diffusivity potholes than the blast-mTBI group (*p* = .032) and the blast-exposed group (*p* = .025). Based on the number of potholes, the blast-exposed group resembled the blast-mTBI group when considered in relation to the blast-unexposed control group.

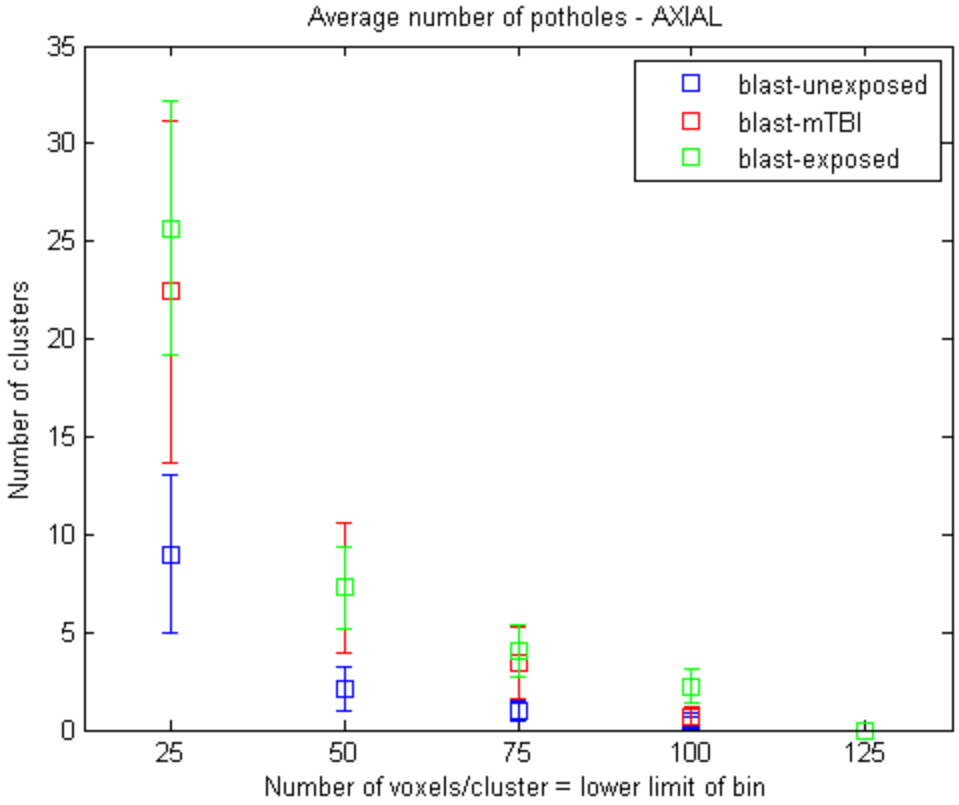


Figure 4. There was a non-significant main effect of group [F(2,42)=2.0, p=.15] on the number of small (25-50 voxel), medium (50-75 voxel), and large (75-100 voxel) potholes, which were defined by voxels with low axial diffusivity values ($z < -2$).

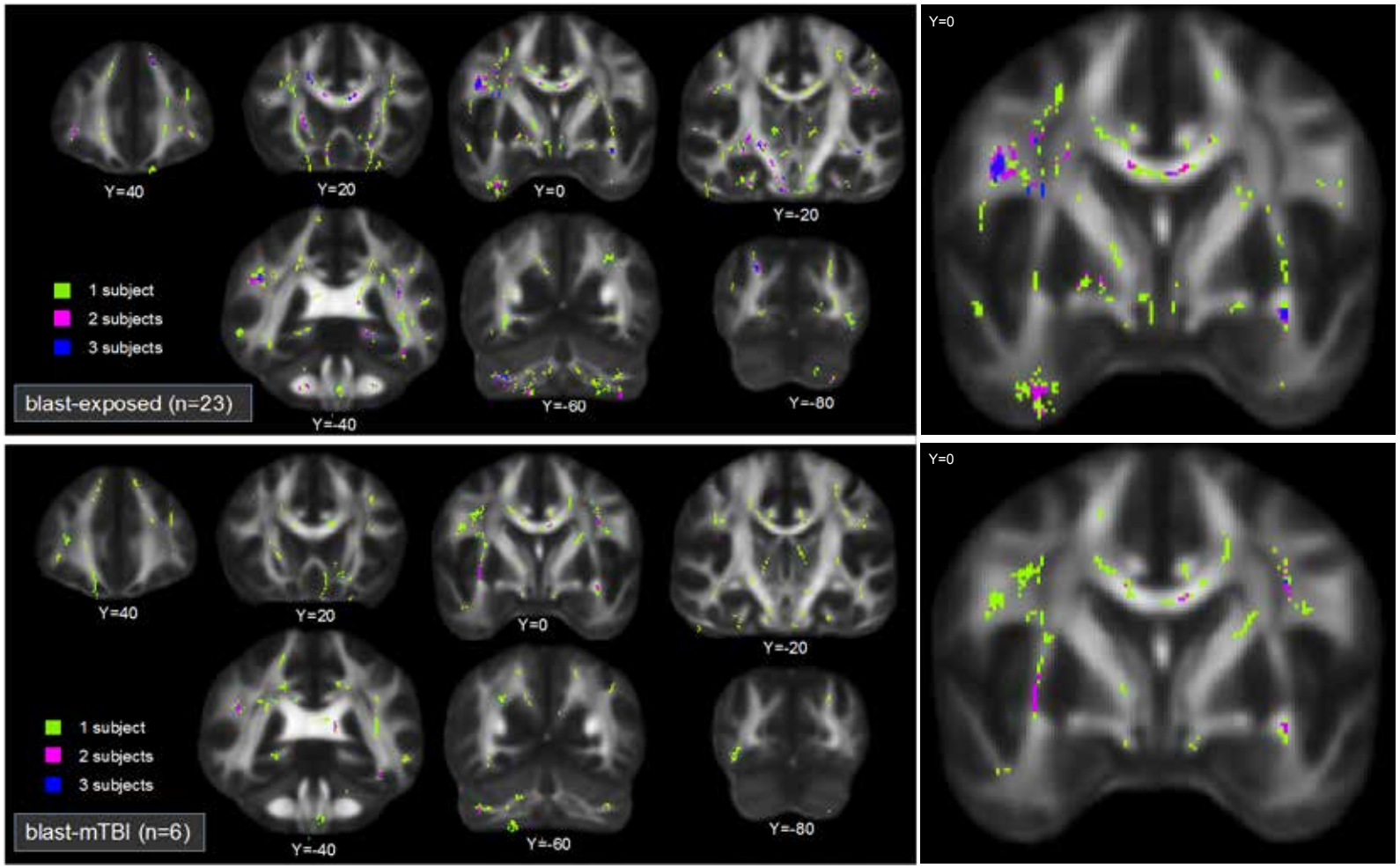
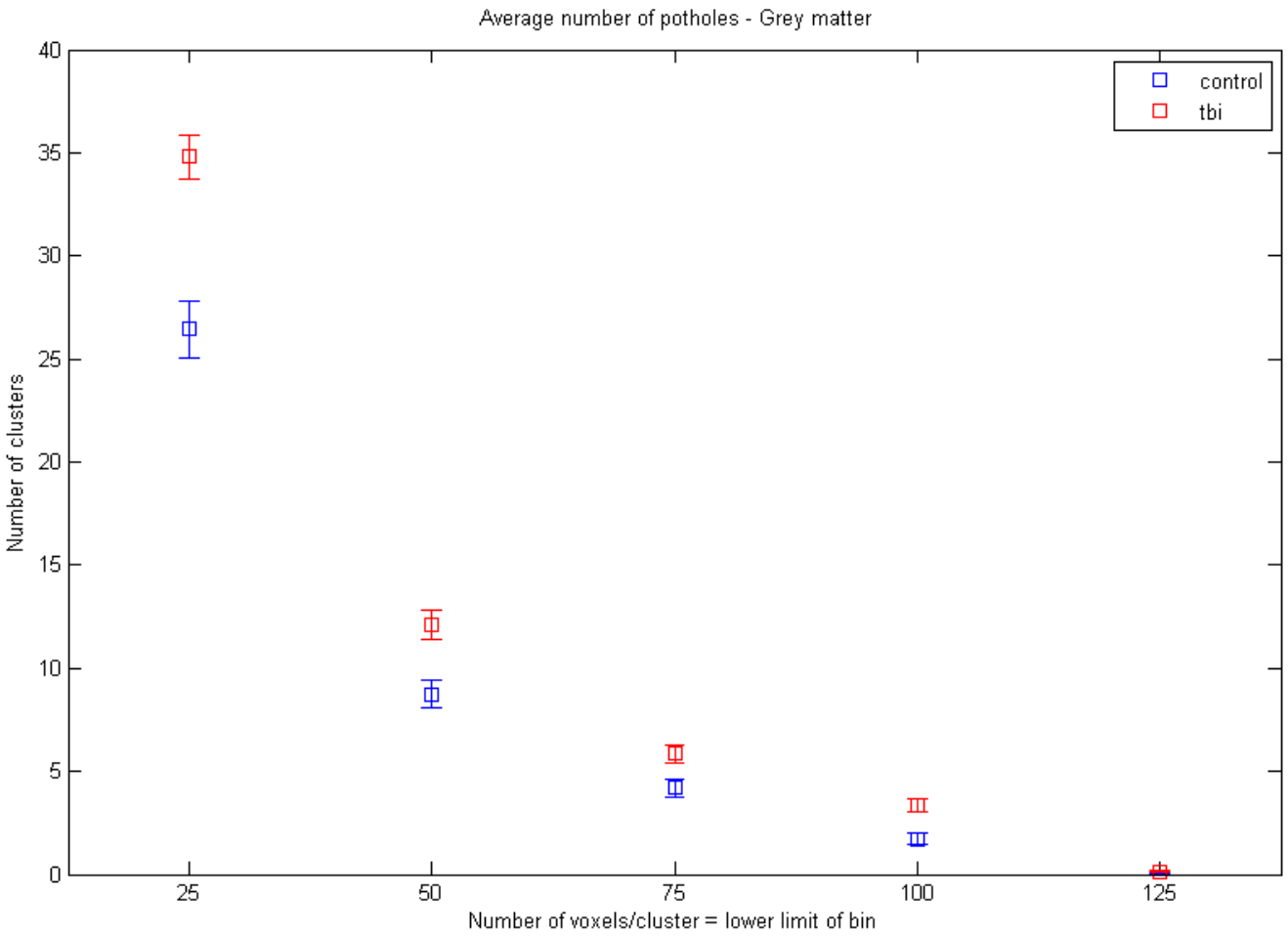


Figure 5. A whole brain voxelwise histogram of potholes over 25 voxels in size demonstrates that potholes in blast-exposed (top panel) and blast-mTBI (lower panel) veterans were distributed in a scattershot spatial distribution. In the voxelwise histogram overlay, lime-green indicates voxel locations where only 1 veteran had a pothole, violet indicates voxel locations were 2 veterans had a pothole, and dark blue indicates voxel locations where 3 veterans had a pothole. Rare instances of voxels had 4-7 subjects (data not shown).

Figure 6. Grey matter potholes with VBM



Conclusions

- Blast-exposed Veterans experience white matter damage that is comparable to mild TBI even in the absence of clinical symptoms.
- The lack of clinically observable TBI symptoms following blast exposure may lead to the erroneous conclusion that little or no damage has occurred to brain tissue and consequently may go unnoticed.
- If confirmed, our findings would argue for an overhaul of the established approach for making diagnoses based on clinically observable symptoms of mild TBI in favor of novel imaging based diagnostic criteria that “look below the surface” for pathology.

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Q & A

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