Non-invasively probing the brain's microstructure with magnetic resonance imaging

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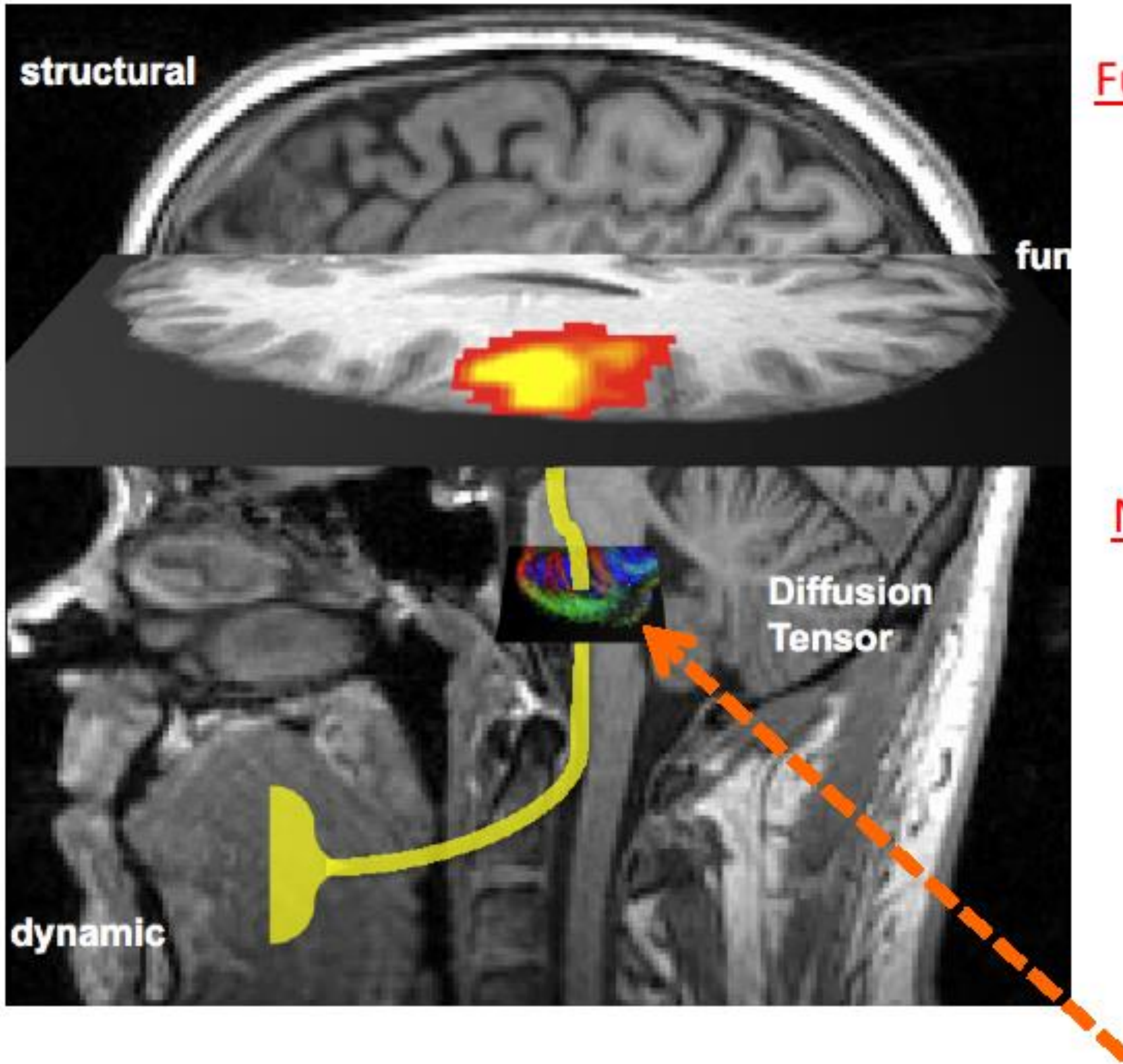
MRI: Many windows into physiological function

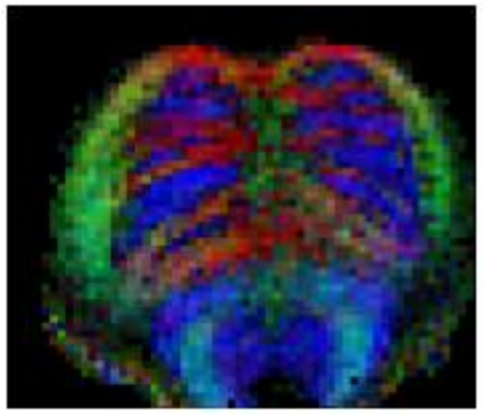
Structural
- Cleft palate
- Oral Cancer

Dynamic Imaging
- Muscular dystrophy
- Muscle changes with age



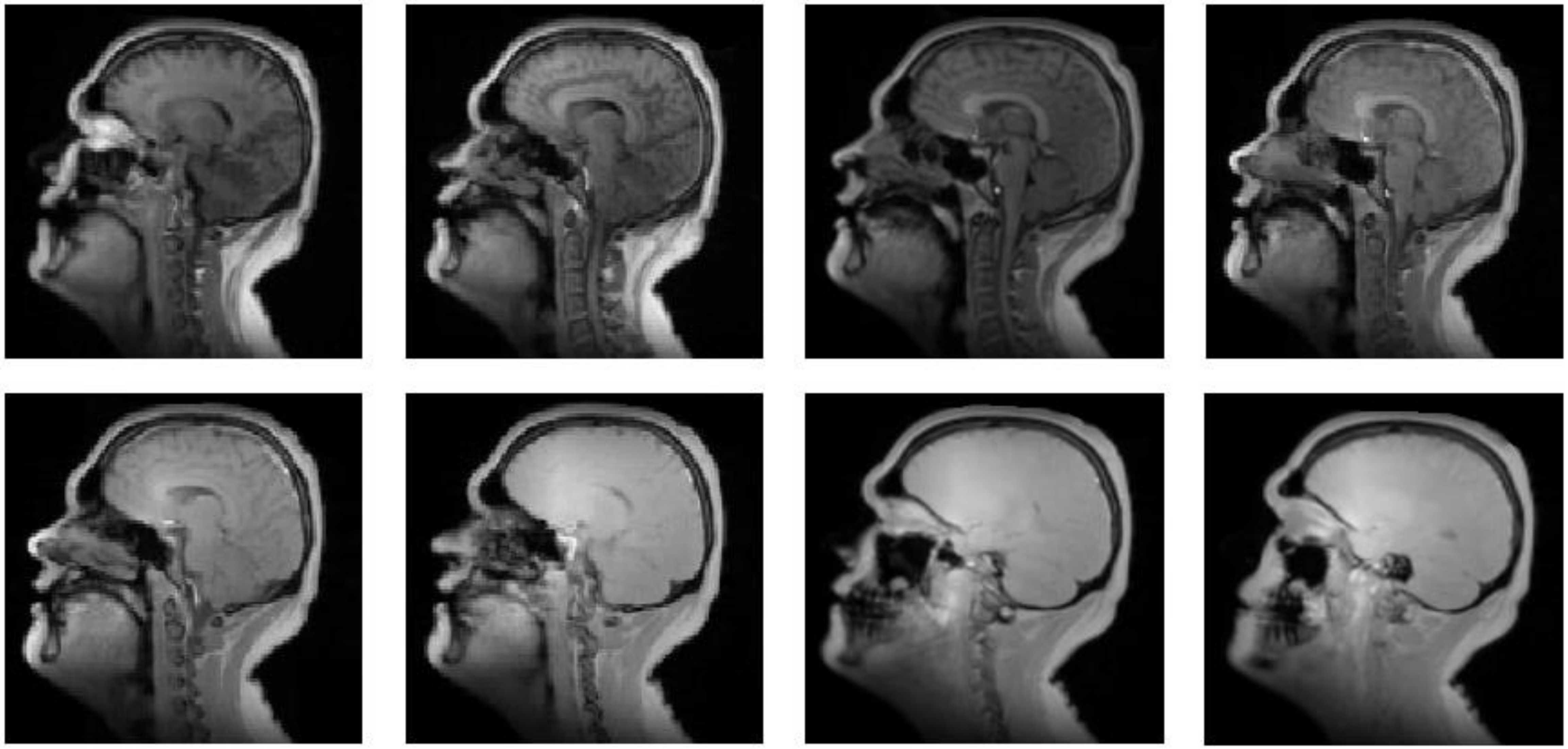
Functional Neuroimaging
- Stroke
- Aging

Neuromuscular Coupling
- MS
- ALS



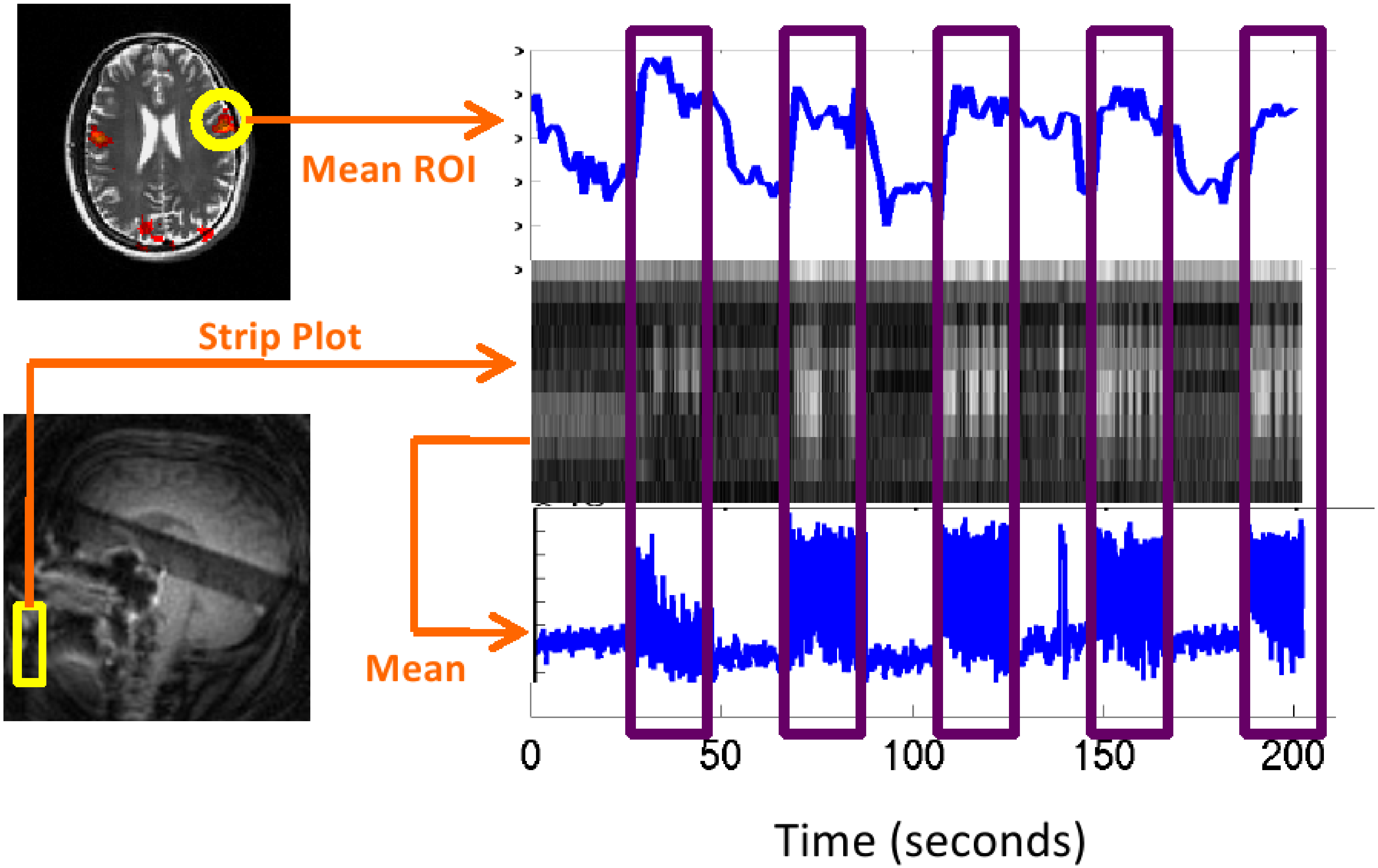
GOAL: Develop quantitative models of motor performance based on physiology descriptions.

Reconstruction Results



- Mid-sagittal views of /loo/ - /lee/ - /la/ - /za/ - /na/ - /za/ sounds.
- An imaging frame rate of **102.2 fps** covering **the entire vocal tract**.
- A spatial resolution of **2.2 mm × 2.2 mm × 6.5 mm** .

SimulScan: block task



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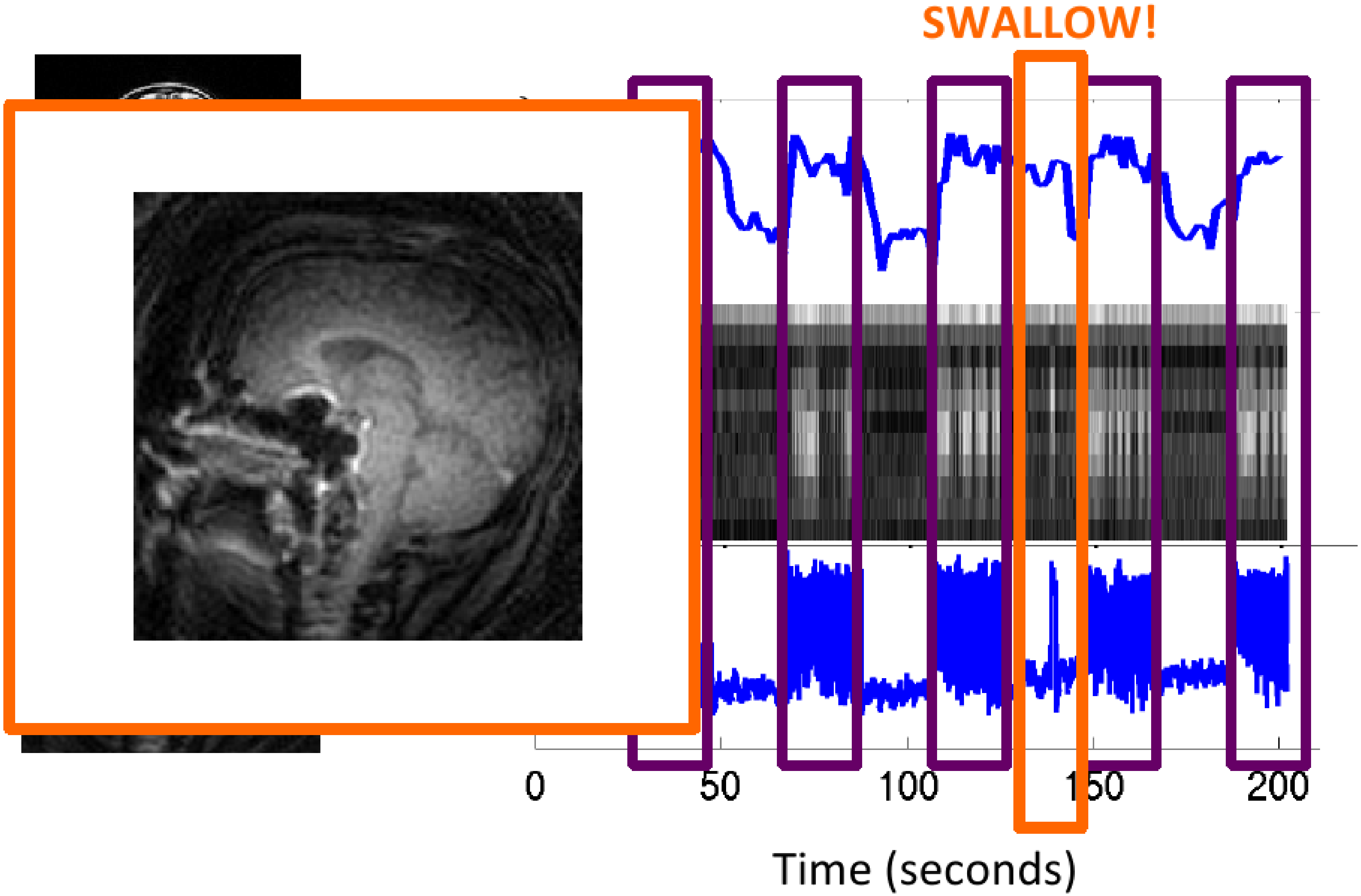

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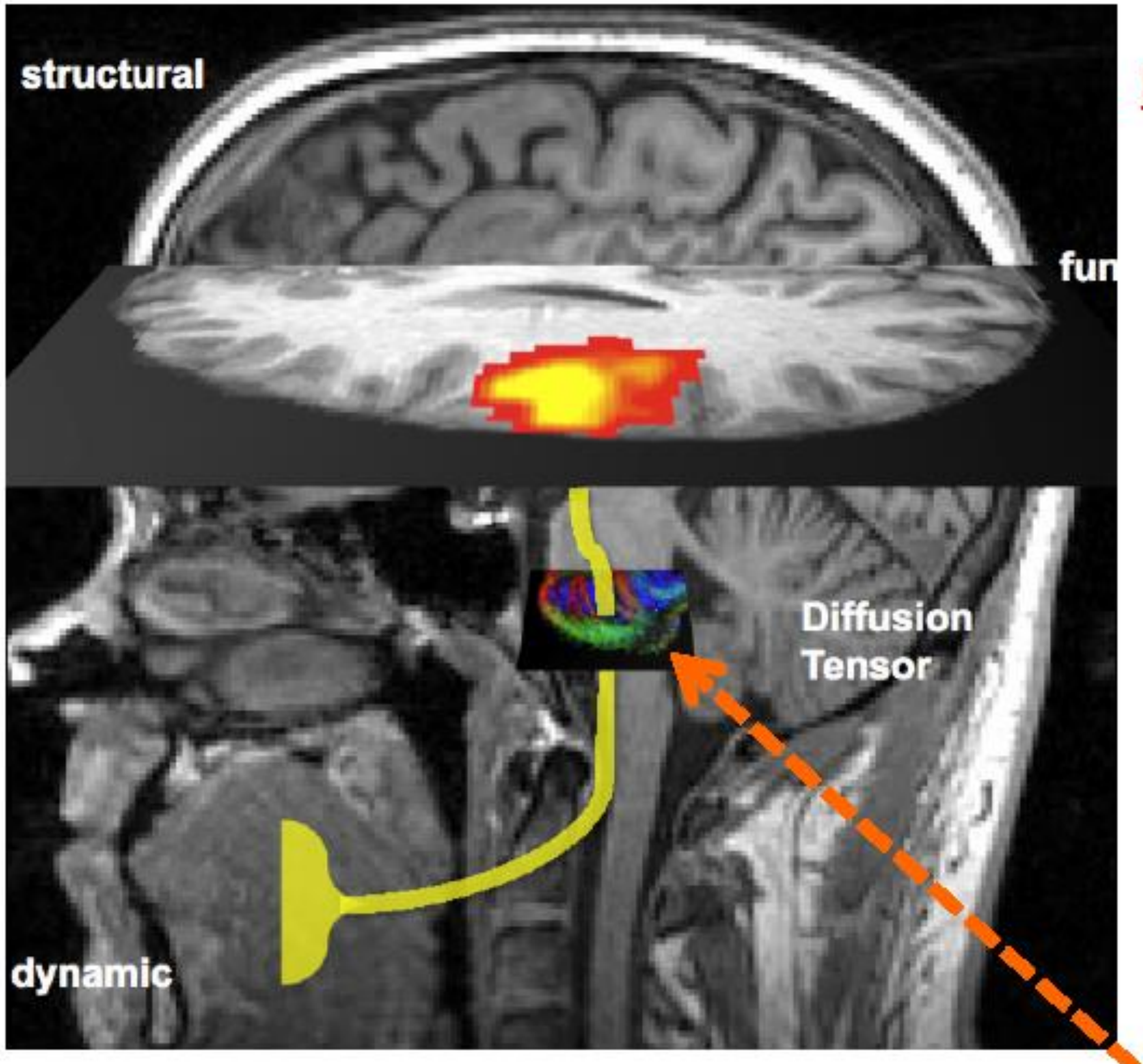

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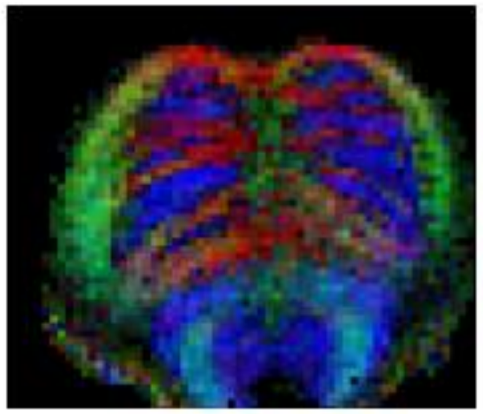
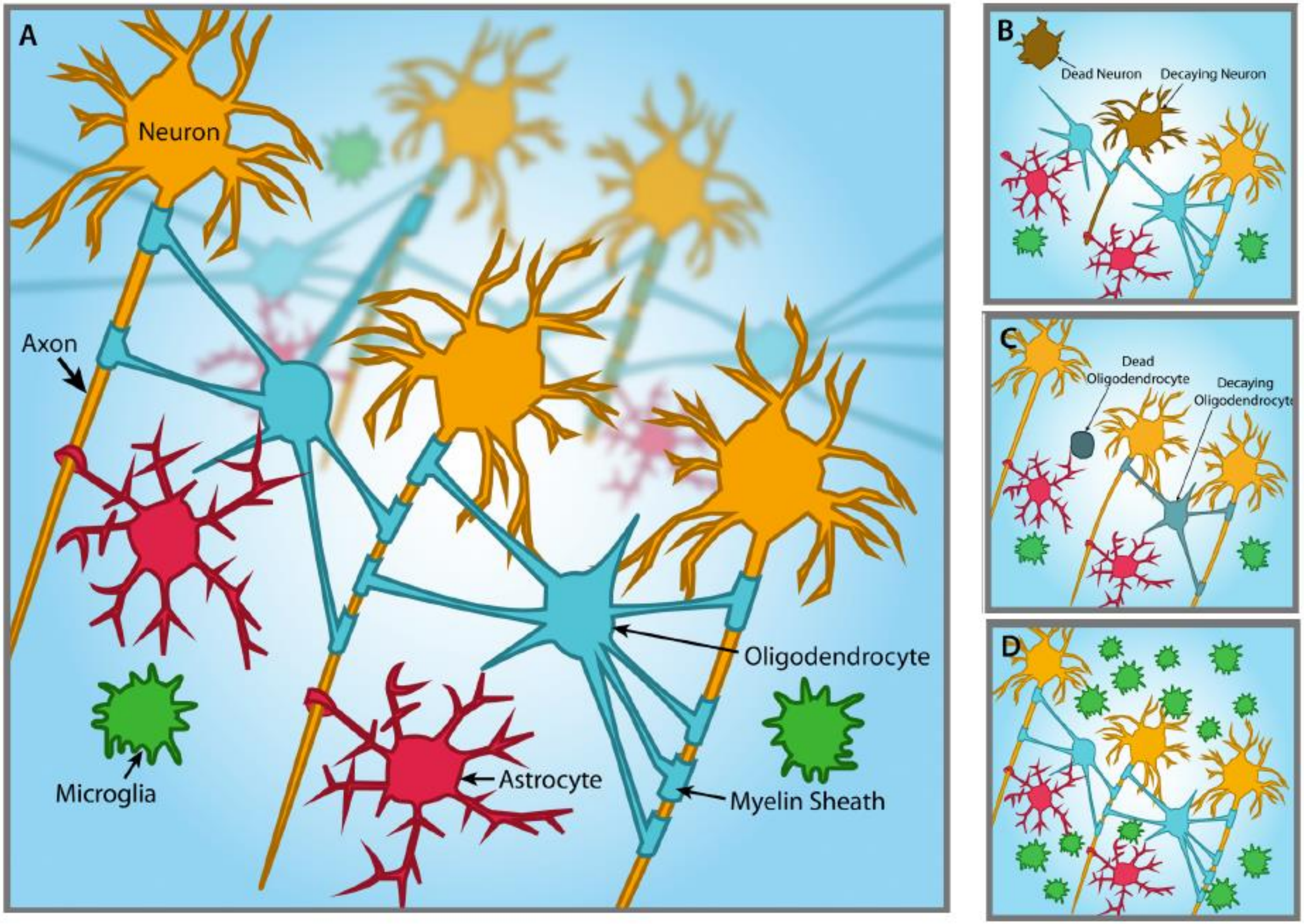


GOAL: Develop quantitative models of motor performance based on physiology descriptions.

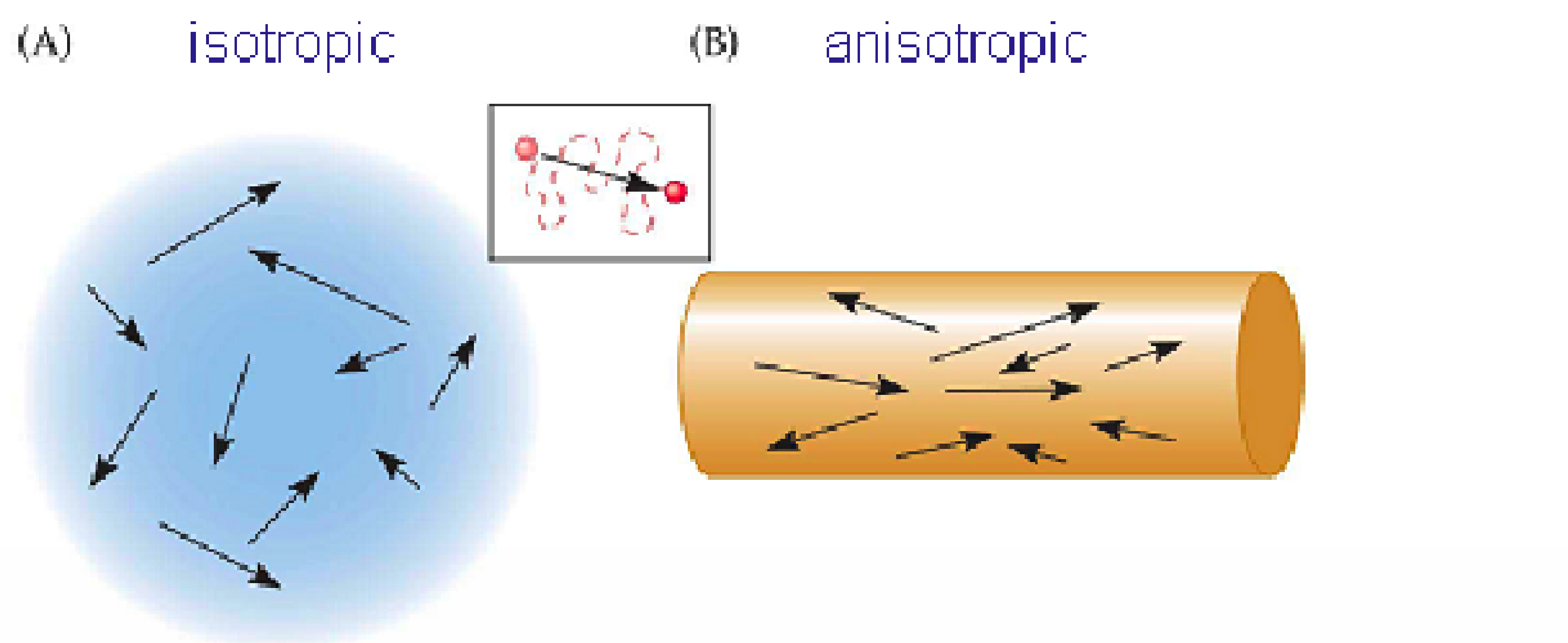
Complementary methods for tissue microstructural information

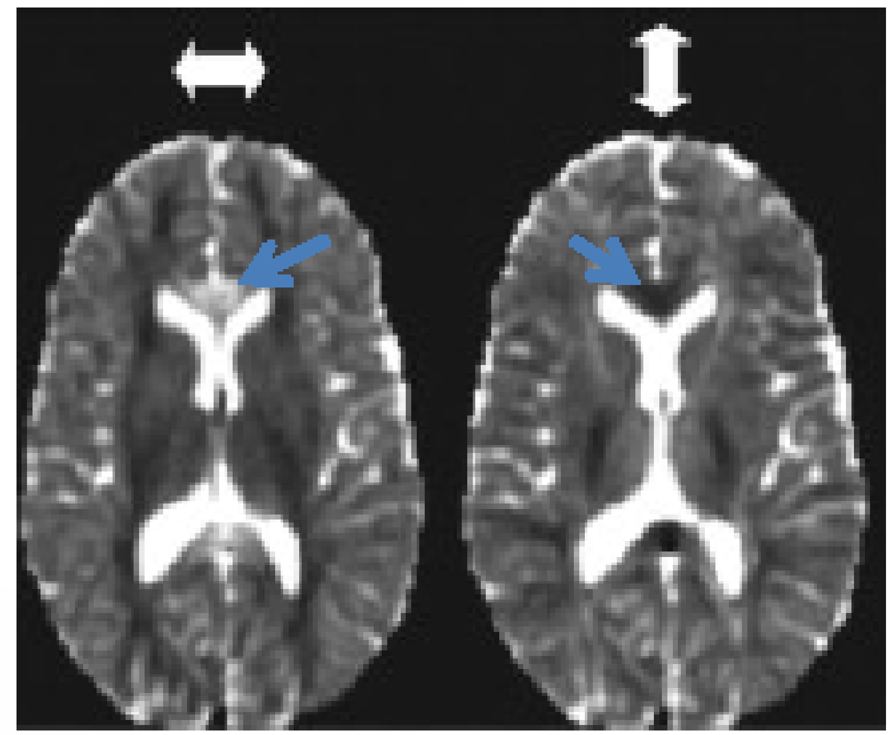
- Diffusion Weighted Imaging
  - tissue microstructure through modeling of the diffusion of water and restrictions (DTI, DSI, q-space, etc)
  - Is commonly used as a biomarker of axonal integrity
- Magnetic Resonance Elastography
  - the mechanical properties of tissues and extracellular matrix

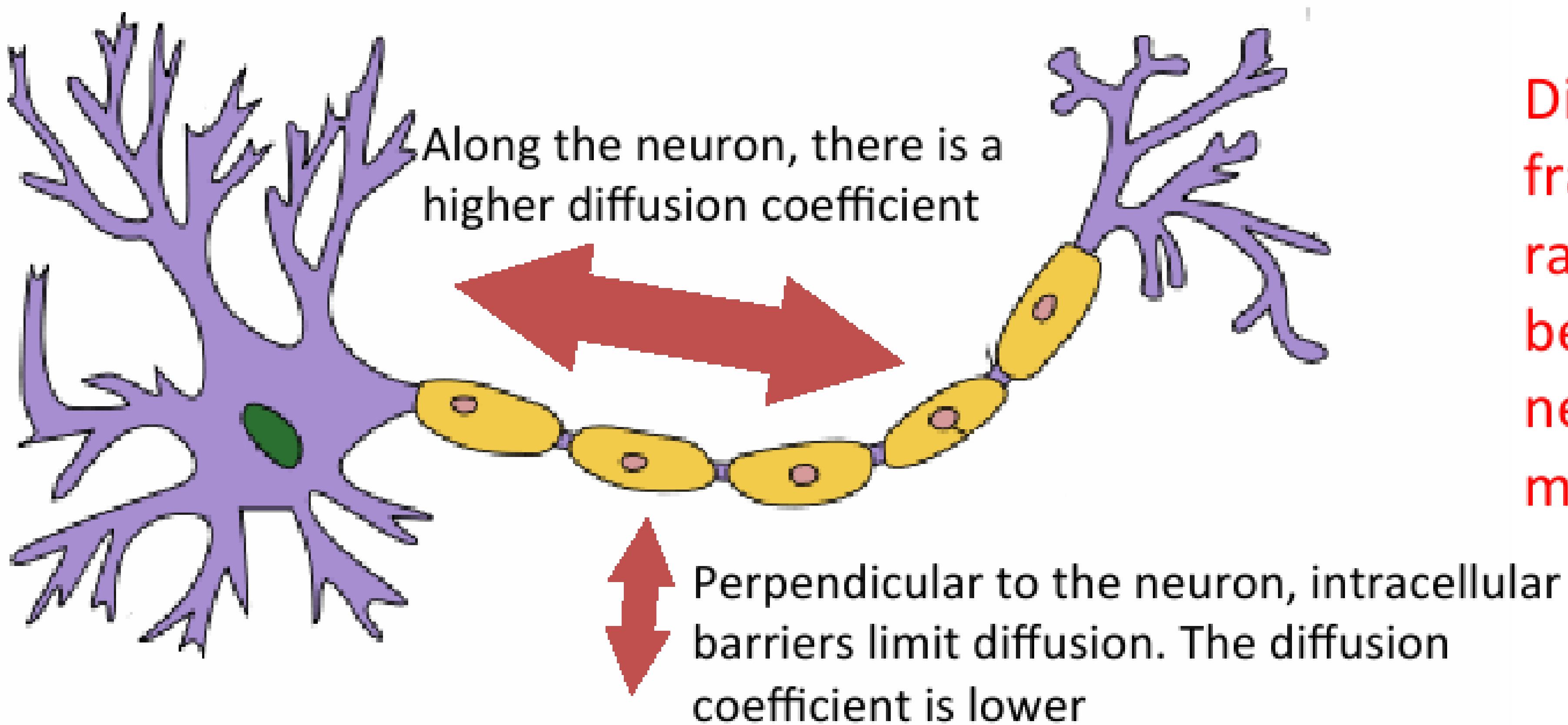


Cartoon by Elise Corbin

Diffusion Imaging



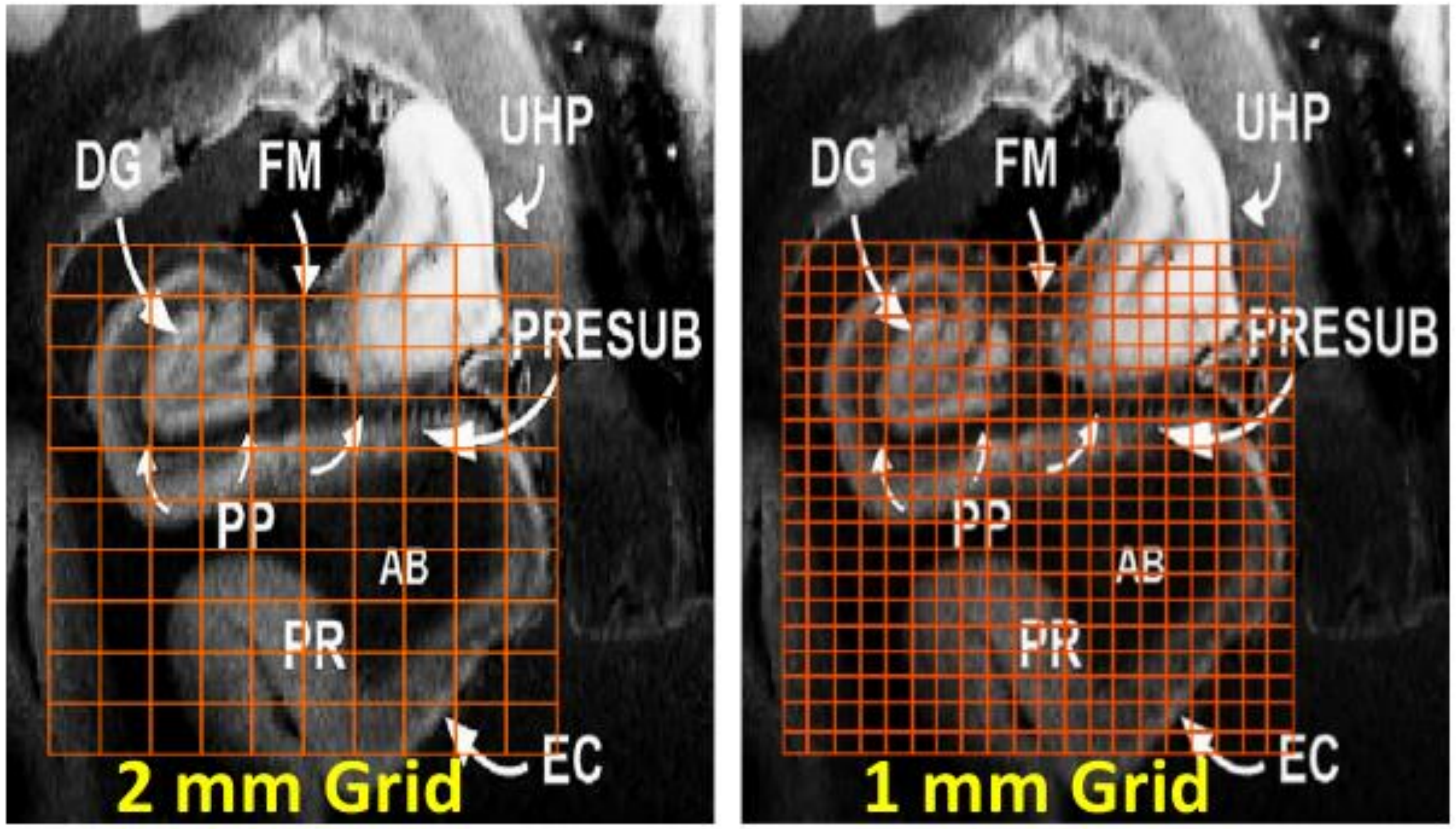




Diffusion metrics such as fractional anisotropy and radial diffusion have been shown to relate to neuronal integrity or myelination.

Need for high resolution diffusion imaging

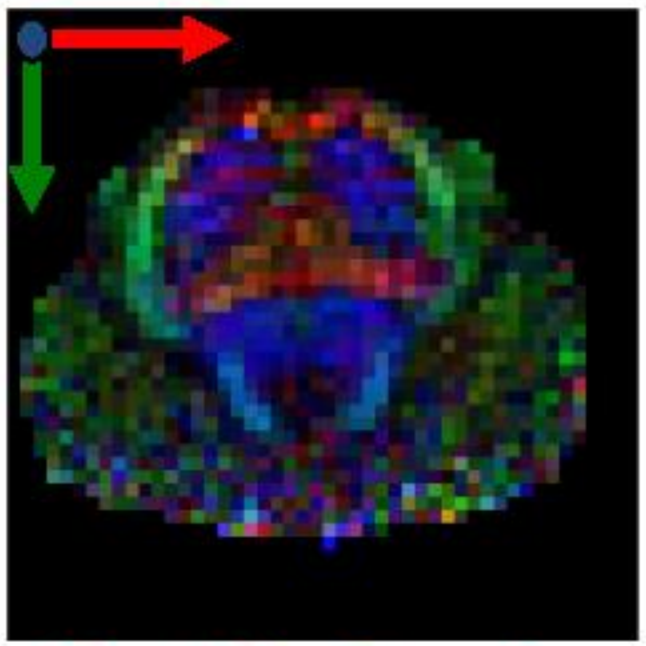
- Interrogation of specific functional information
  - Investigate specific neural connections for functional declines with aging
  - Structural and functional separation of networks
- Resolve complex geometries
  - Crossing fibers
  - Fine structures
  - Reduce partial volume effects to maintain sensitivity



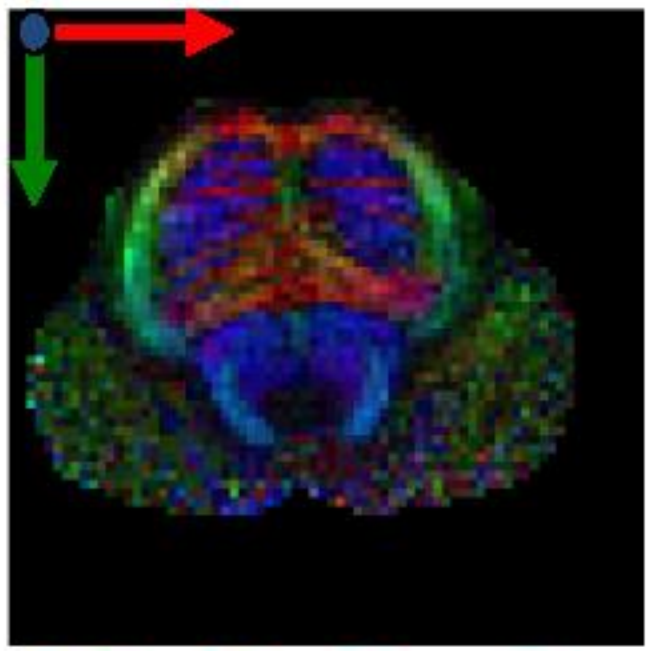
Underlying image from Augustinack, 2010

Reduction of Partial Volume Effects

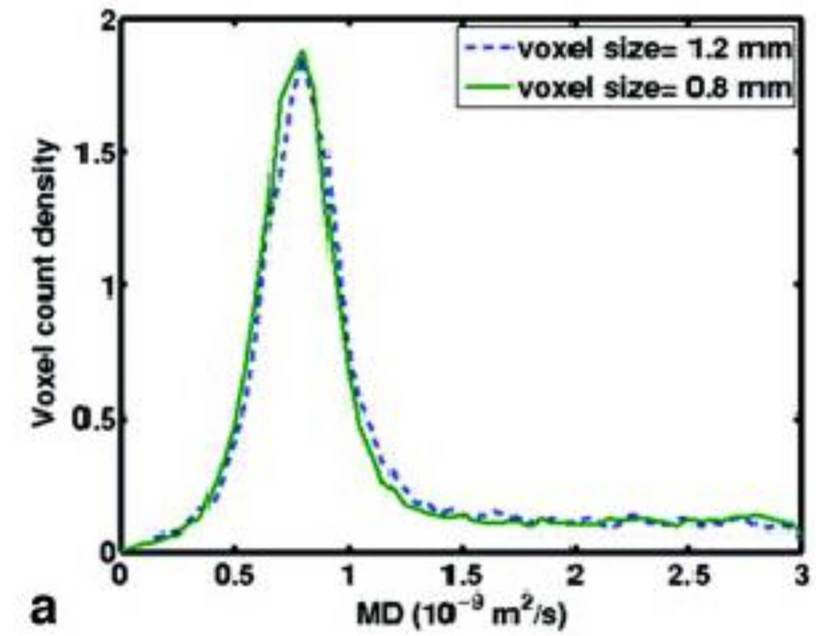
- average diffusion properties within an imaging voxel
- heterogeneity within voxels: multiple fibers
- precision depends on resolution / diffusion encoding scheme

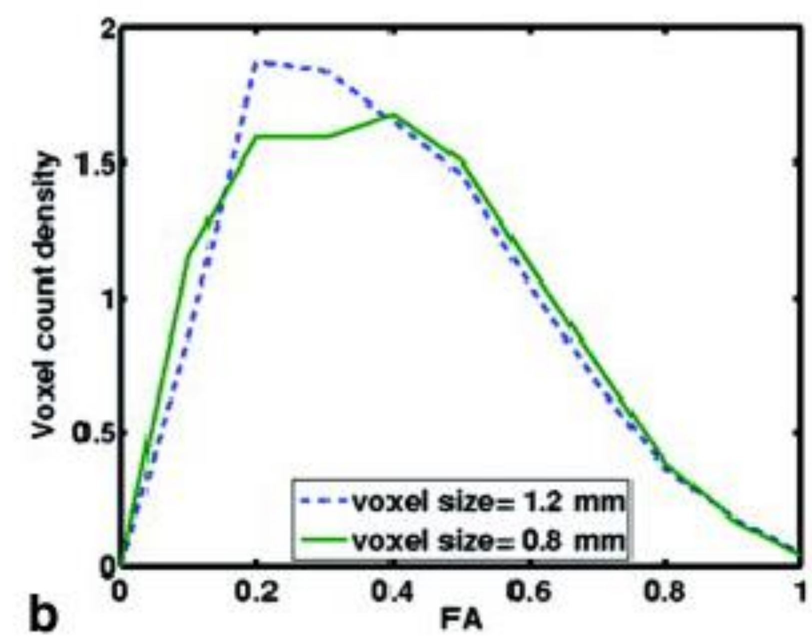


$1.2 \times 1.2 \times 3\ mm^3$

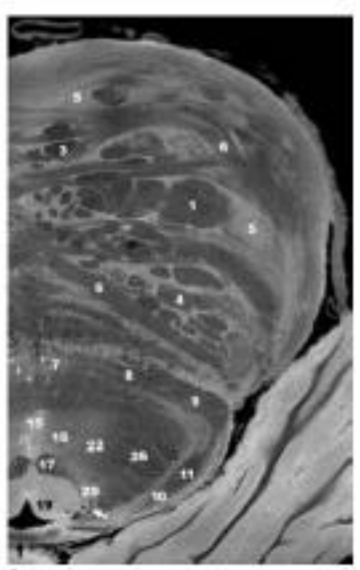


$0.8 \times 0.8 \times 3\ mm^3$





Karampinos, et al., MRM, 2009



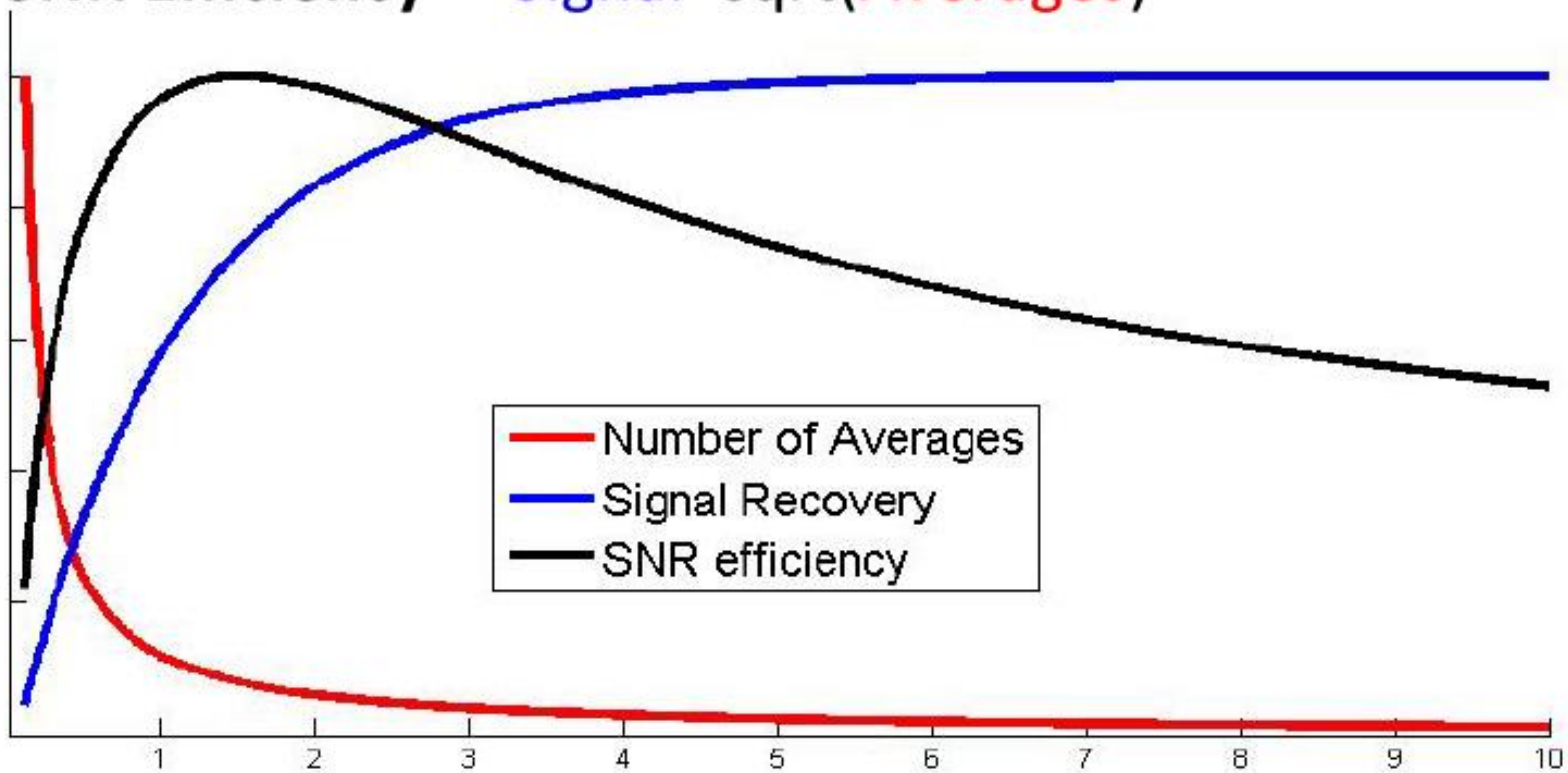
Duvernoy's Atlas of Human Brain Stem and Cerebellum, 2009.

Challenges to Achieving Higher Resolutions

- Diffusion imaging is traditionally a low SNR technique
  - SNR is proportional to voxel size
  - Example: Going from a 2x2x2 mm^3 voxel to a 1x1x1 mm^3 voxel
    - Voxel size is 1/8 the size, so it has 1/8 the SNR.
    - Need 64 averages at 1x1x1 mm^3 to have the same SNR as the 2x2x2 mm^3.
- Subject motion – nearly all diffusion imaging is single shot due to motion induced phase error challenge
- Long data acquisition readouts
  - Magnetic Field Inhomogeneity

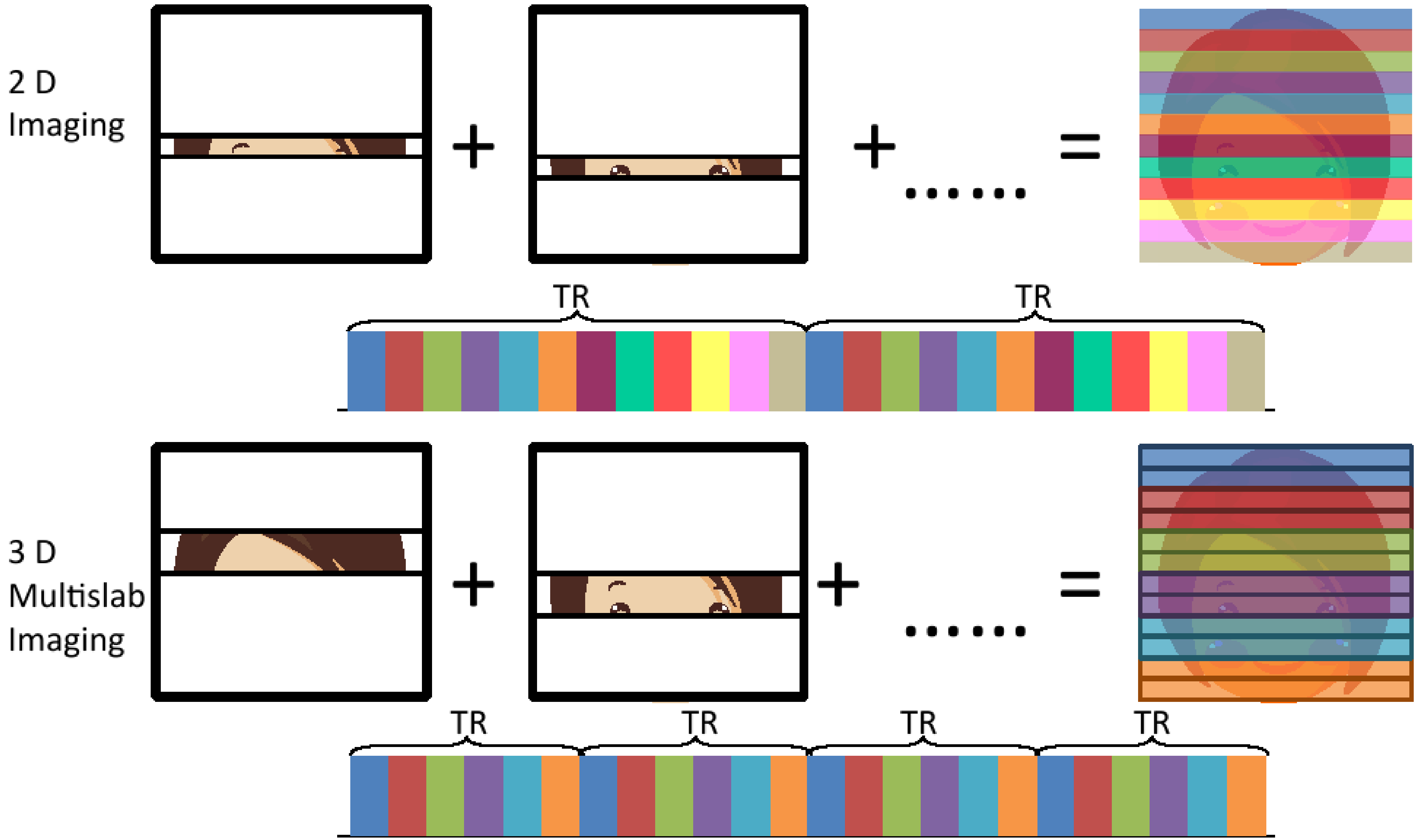
SNR Considerations

- How often should we acquire data for an image (TR)?
  - Acquiring data faster allows more averaging to be done (Averages $\propto$ 1/TR)
  - Acquiring slower allows more time for signal recovery.
    (Signal $\propto 1\text{-}2e^{-(TR-TE/2)/T1} + e^{-TR/T1}$)
  - **SNR Efficiency** $\propto$ Signal*sqrt(Averages)



How often data is collected (TR in Seconds)

3D multi-slab allows an SNR optimal TR to be used



Multi-shot → motion-induced phase errors

- Small coherent motions in each shot result in a random phase
- Adding shots together can result in signal cancellations

Cardiac gating: no pulsation-induced phase errors. Rigid-body motion only. Requires navigation in acquisition.

Ideally:

Non diffusion weighted image →

$$I_0(\mathbf{r}) = |I_0(\mathbf{r})| e^{j\varphi(\mathbf{r})}$$

Ideal diffusion weighted image →

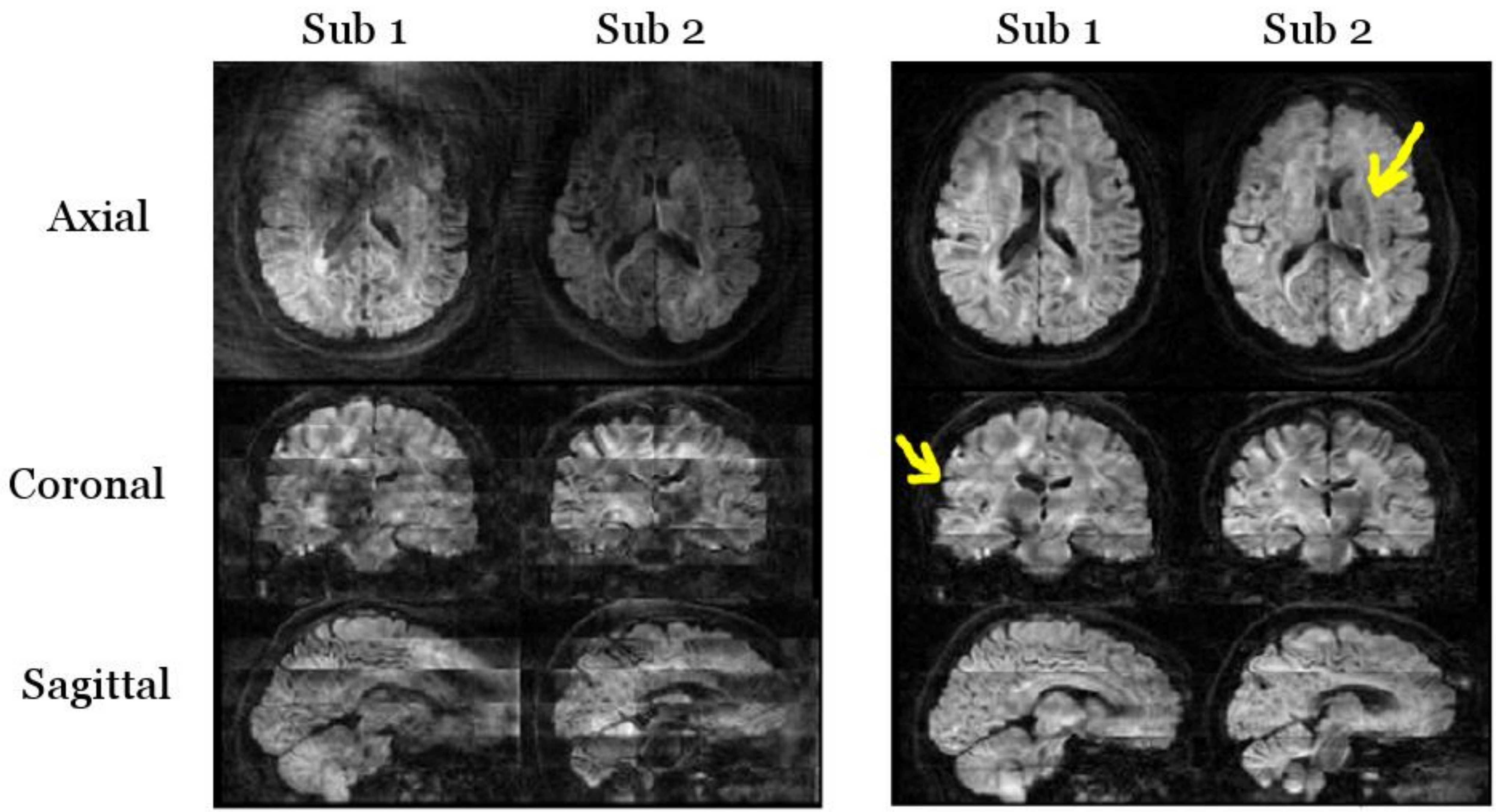
$$I_b(\mathbf{r}) = |I_b(\mathbf{r})| e^{j\varphi(\mathbf{r})}$$

To solve for linear phase error, solve non-linear least squares problem (need navigator data, minimize over **a**, a_o):

$$\tilde{R}(\mathbf{a}, a_0) = \sum_{\mathbf{r}} \left| \tilde{I}_b(\mathbf{r}) - |I_b(\mathbf{r})| e^{j\left[\angle I_0(\mathbf{r}) + (\mathbf{a}\cdot\mathbf{r}) + a_0\right]} \right|^2$$

Van et al, IEEE TMI 2011.

Results: 3D multi-slab DW Images

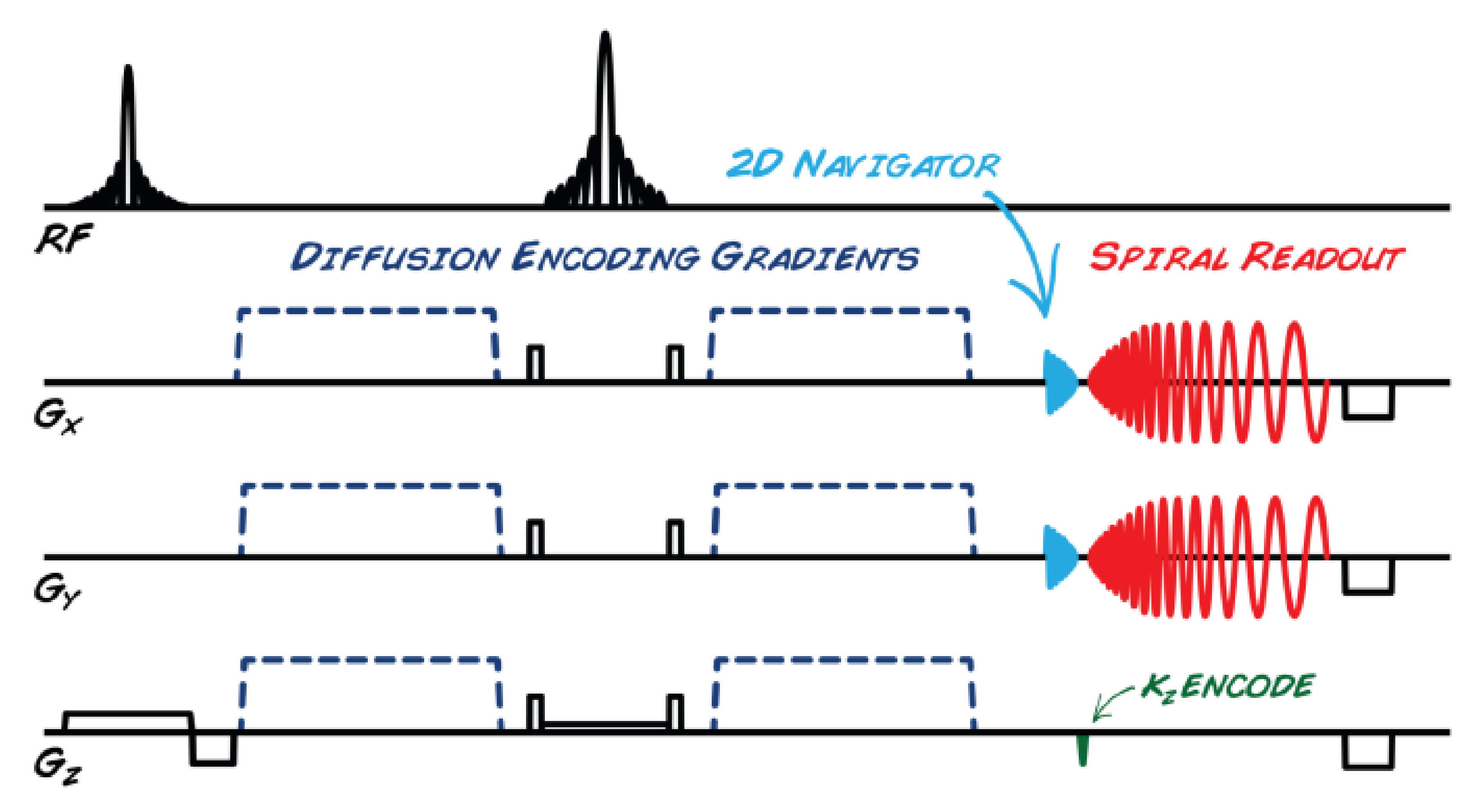


No motion correction

With correction for motion induced phase errors

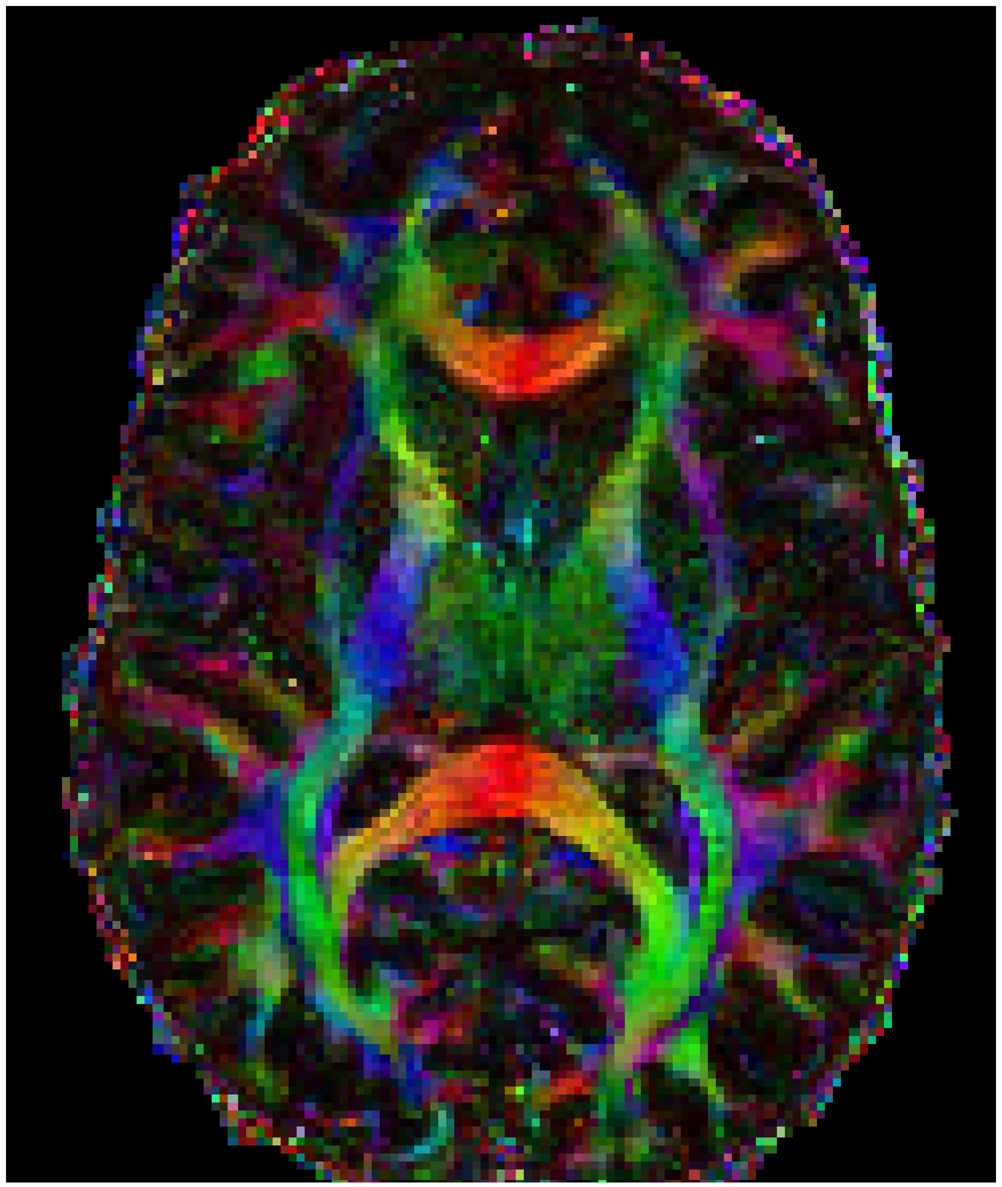
2x2x2 mm^3 Resolution

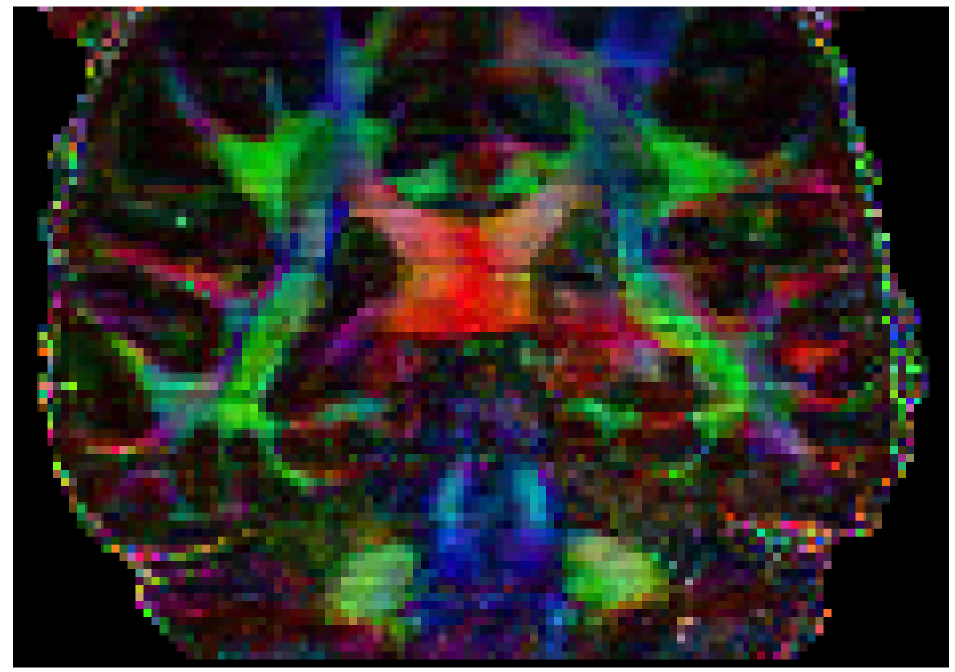
Imaging Acquisition

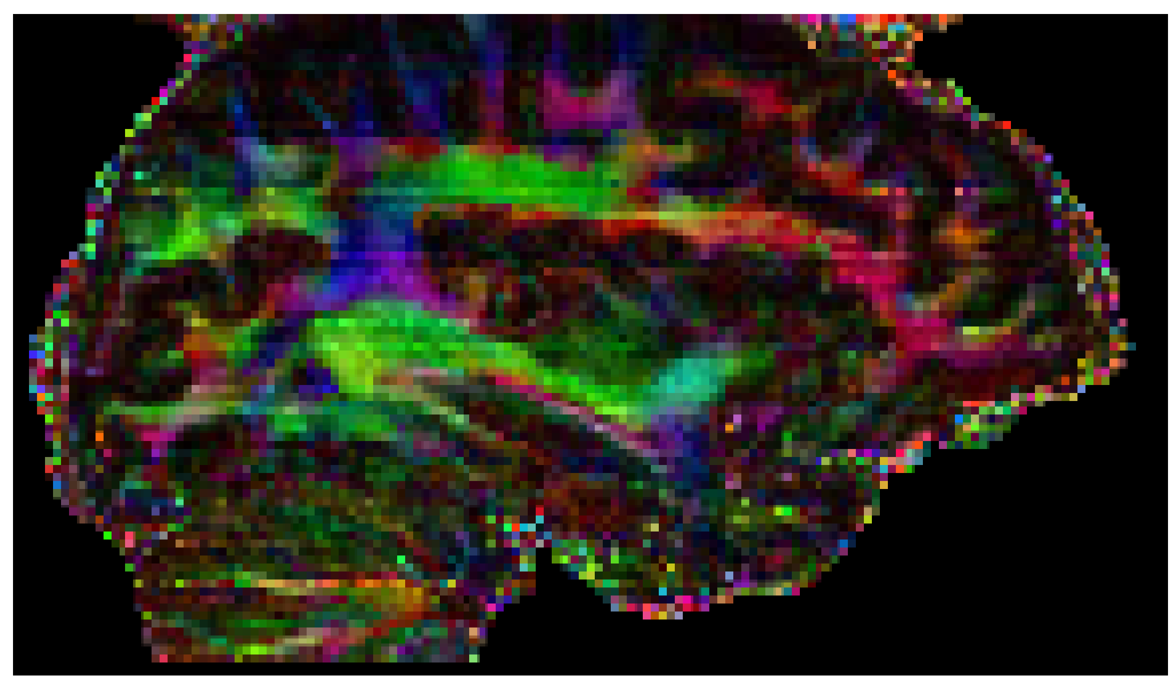


- No limits on the number of shots that can be used
- The navigator does not add any additional time to the acquisition of TR
- A spiral readout allows for a short echo time

1.25 mm FA Images







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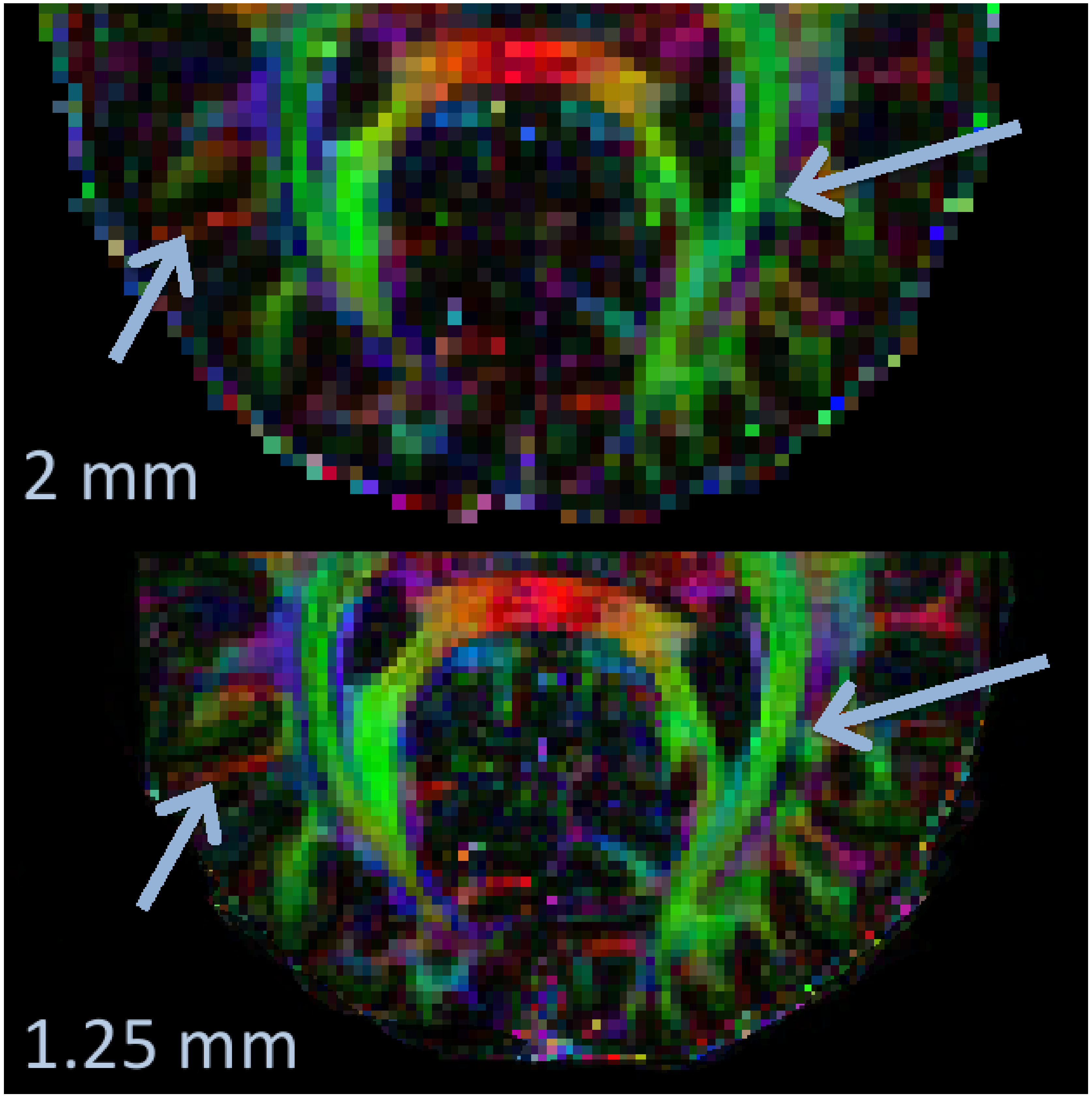
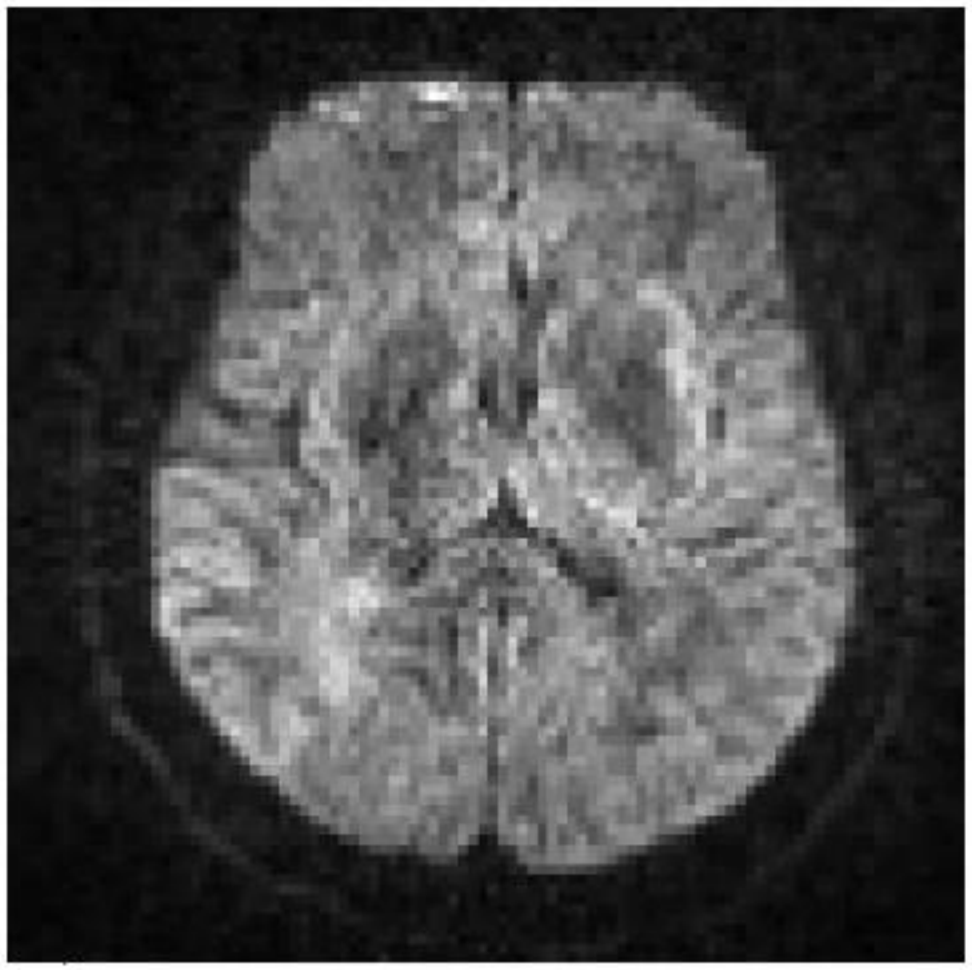


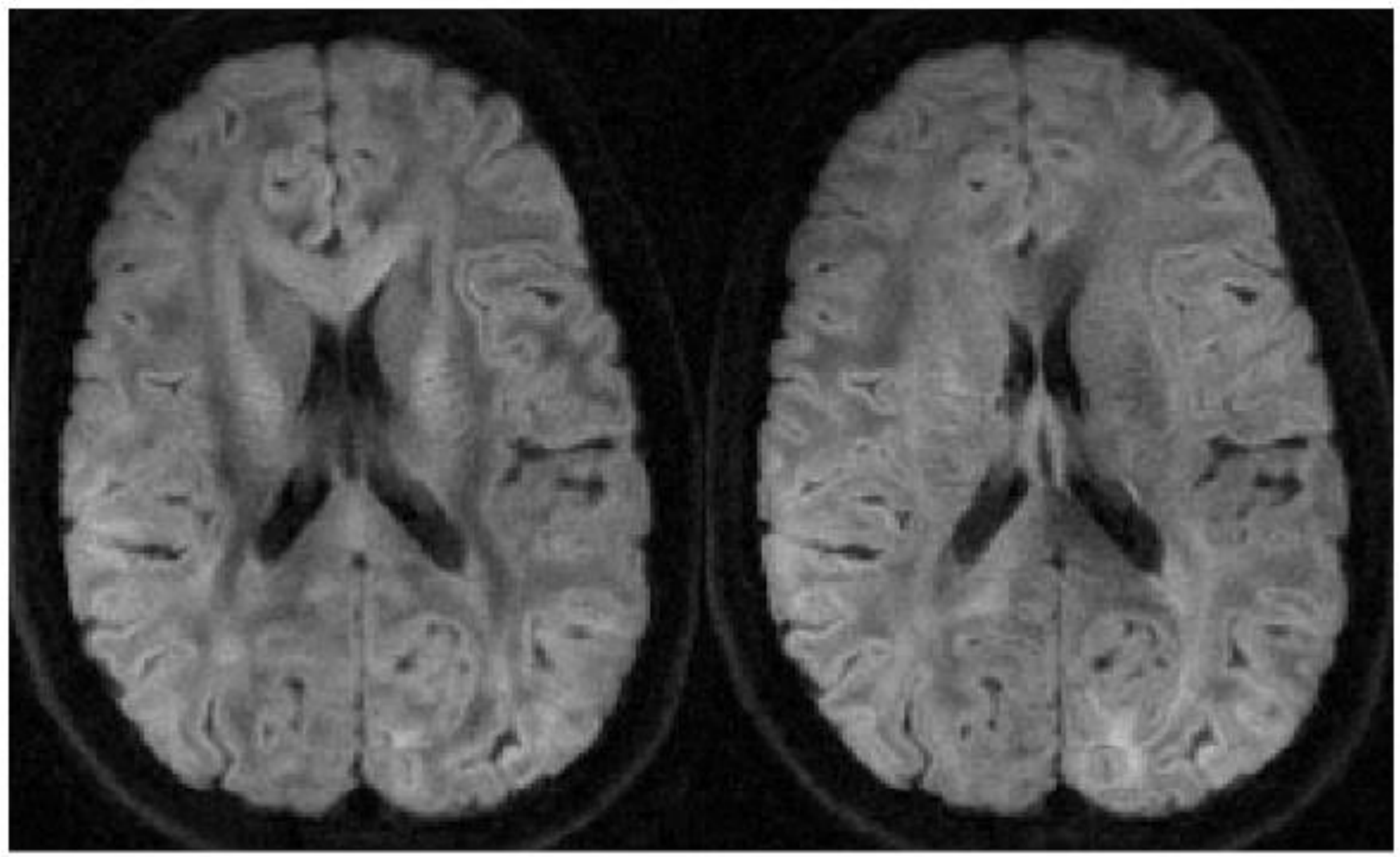
At high resolutions, fine structures separate and become visible

Results: 1 mm Isotropic Resolution Diffusion Weighted Images

1.88x1.88x2 mm^3 DWI
Using standard 2D methods



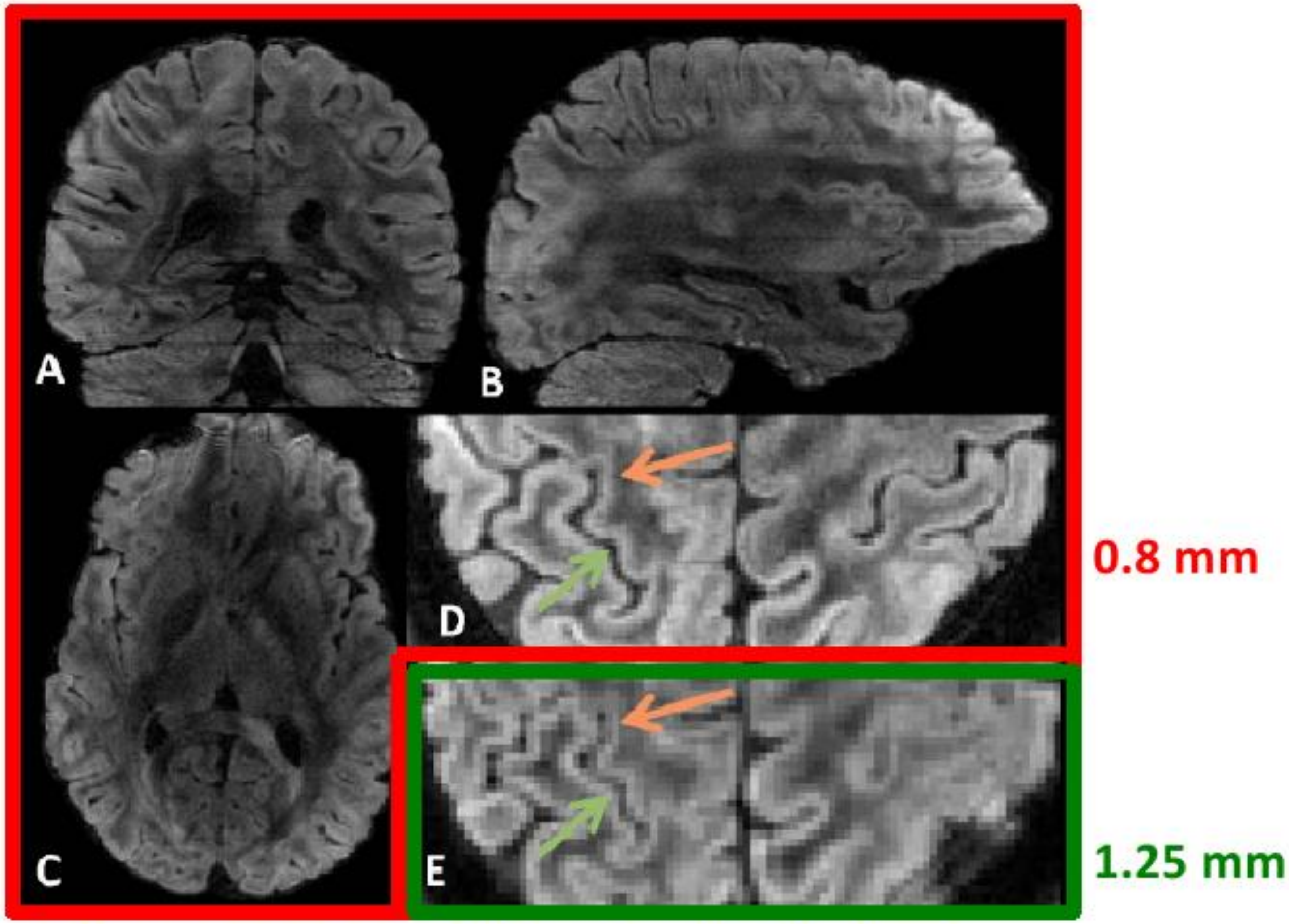
1x1x1 mm^3 DWI
Using proposed multi-slab technique



2 different diffusion directions are shown

Pushing the limits: 0.8 mm isotropic whole brain diffusion imaging

Exceeding spatial resolution of currently used structural scans, but with restricted diffusion information.

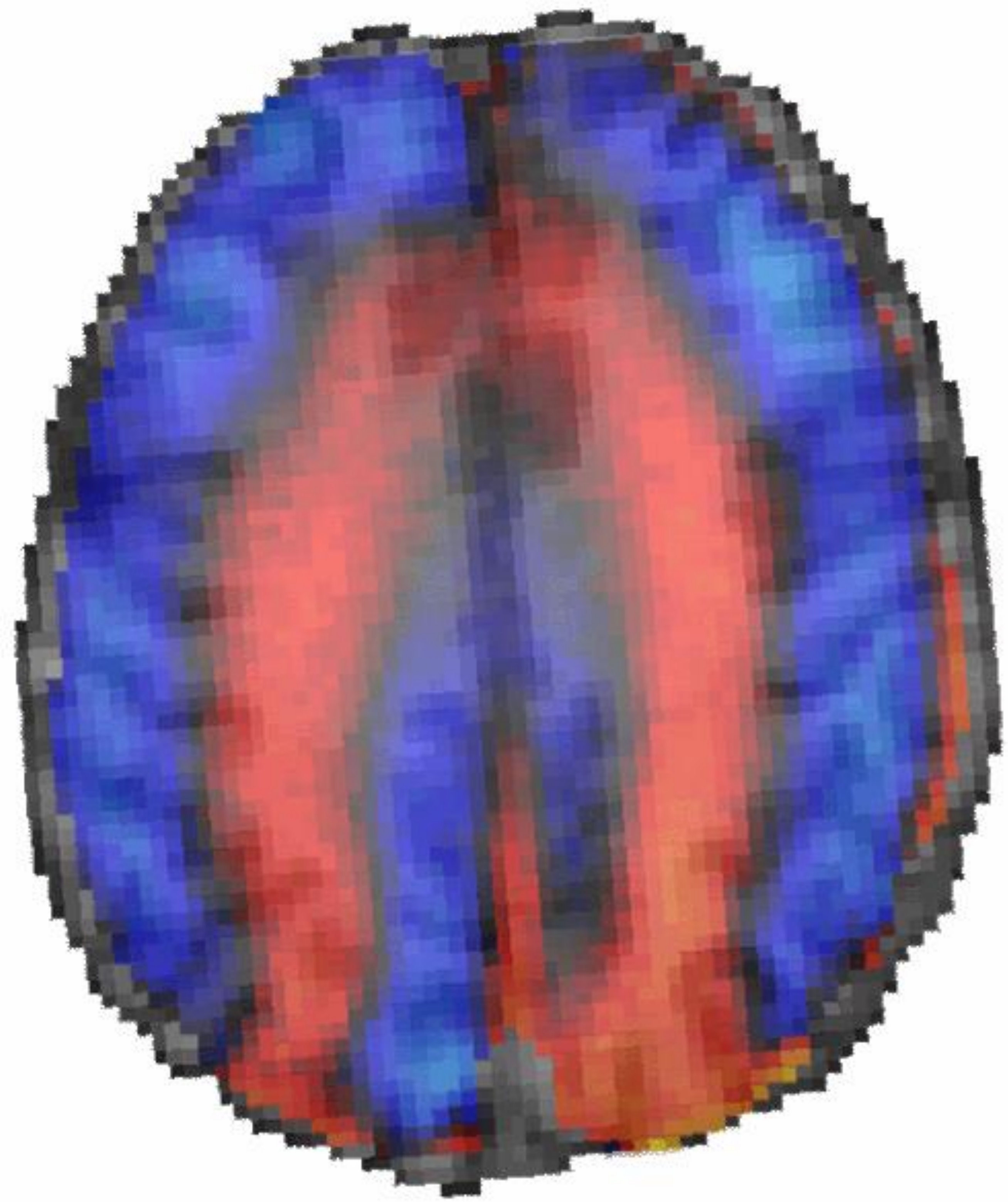


0.8 mm isotropic DWI, b-value 1000 s/mm^2

0.512 µL voxel volume

Holtrop and Sutton. Inter Soc. Magn Reson Med, 2013.

Local Mechanical Properties of White Matter Structures in the Human Brain with Magnetic Resonance Elastography (MRE)



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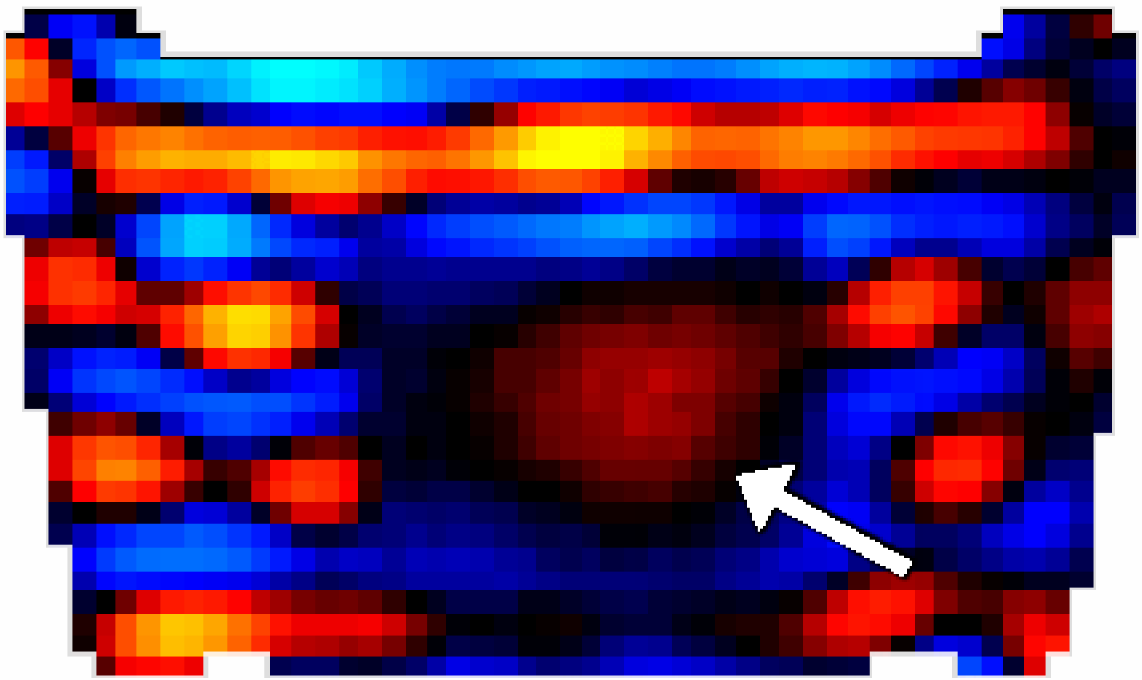
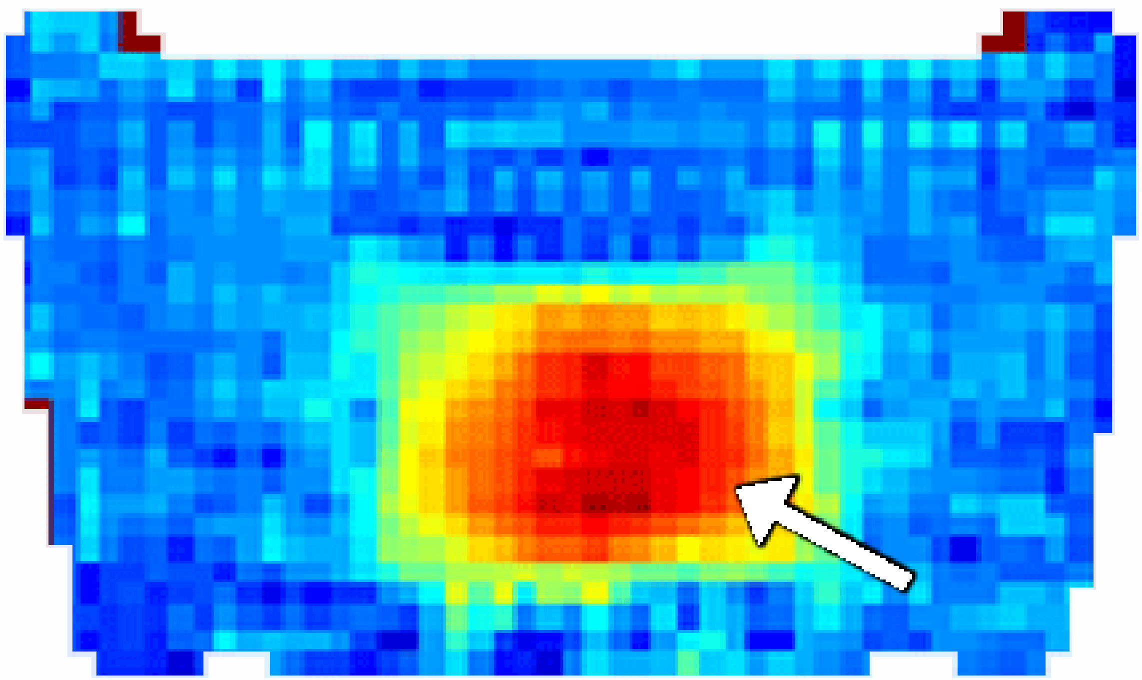


Propagating Shear Waves



Estimated Shear Stiffness

MRE is a ***non-invasive*** shear wave imaging technique for probing the ***mechanical properties*** of biological tissues

The brain gets ***softer*** (less stiff and less viscous) in neurodegeneration:

- Alzheimer's disease
- multiple sclerosis
- normal pressure hydrocephalus
- normal physiological aging

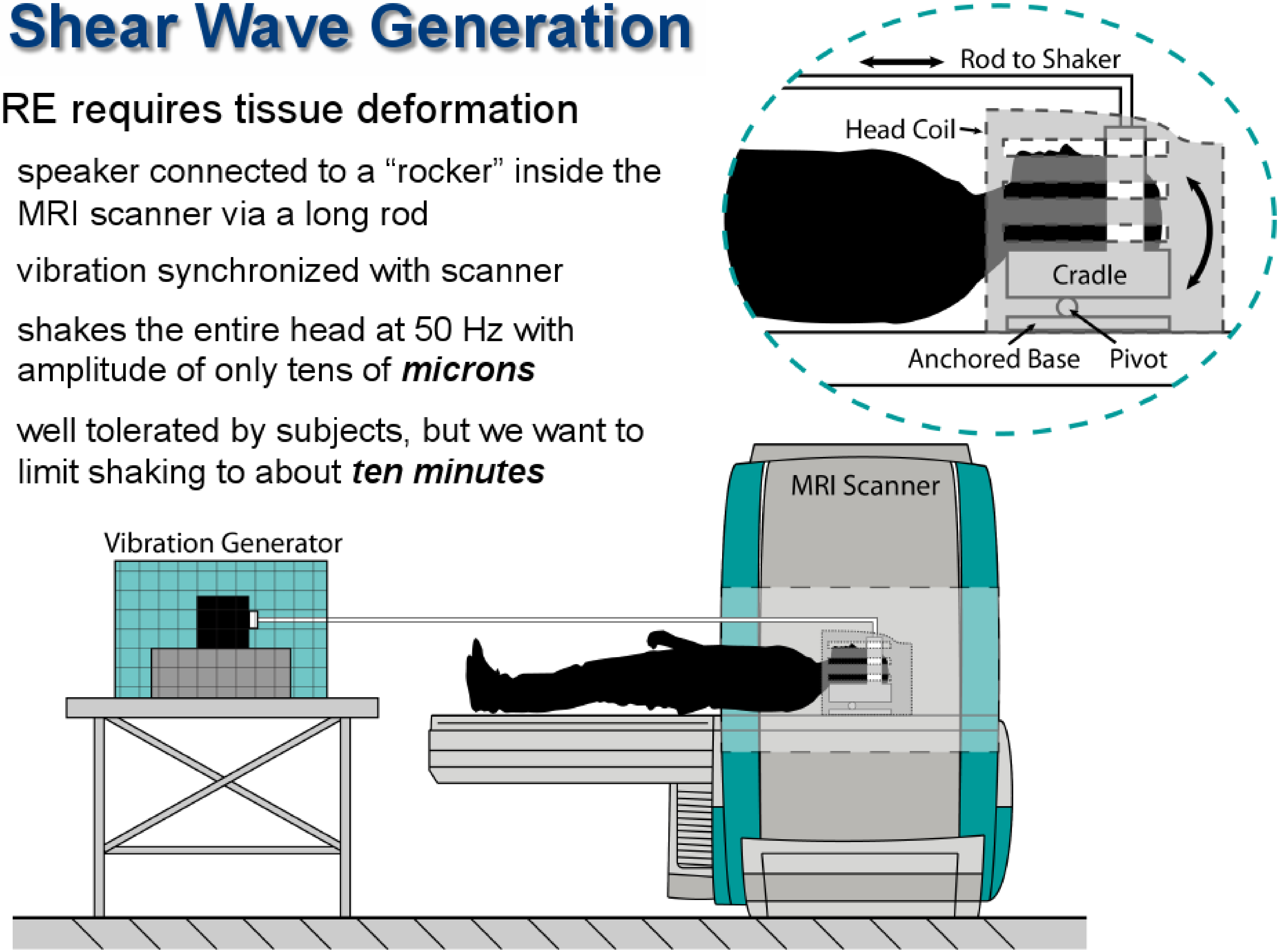
Typical MRE experiment:

- shear deformation with external actuator
- phase contrast imaging of shear waves
- inversion algorithm for property estimation

Shear Wave Generation

MRE requires tissue deformation

- speaker connected to a "rocker" inside the MRI scanner via a long rod
- vibration synchronized with scanner
- shakes the entire head at 50 Hz with amplitude of only tens of ***microns***
- well tolerated by subjects, but we want to limit shaking to about ***ten minutes***



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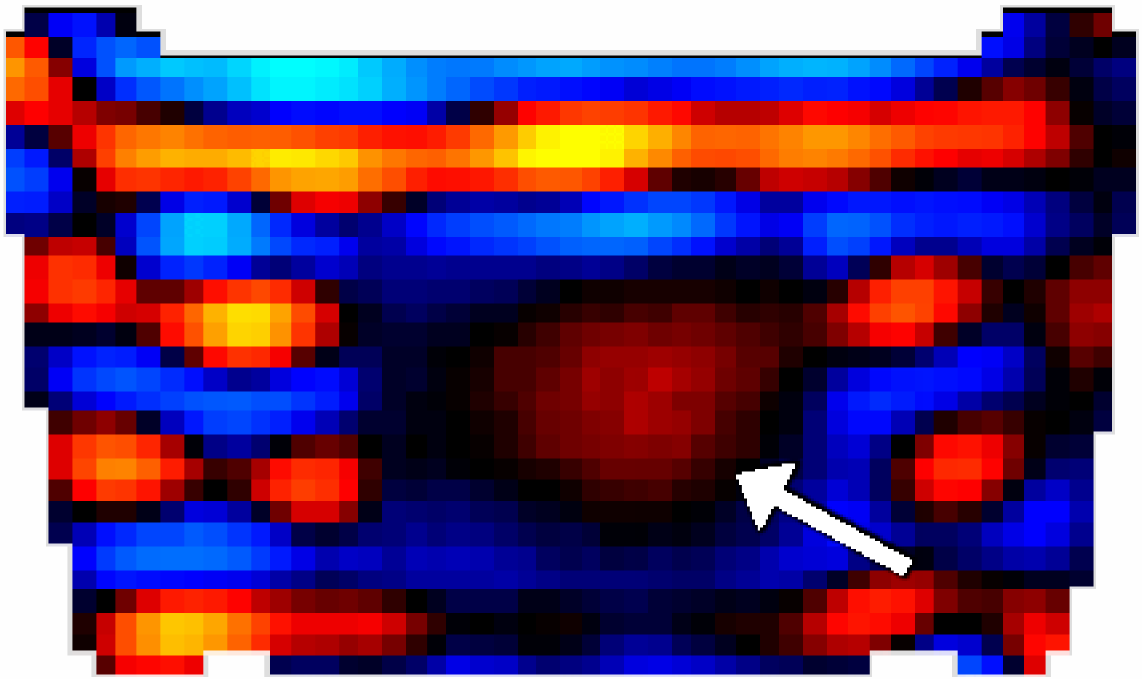

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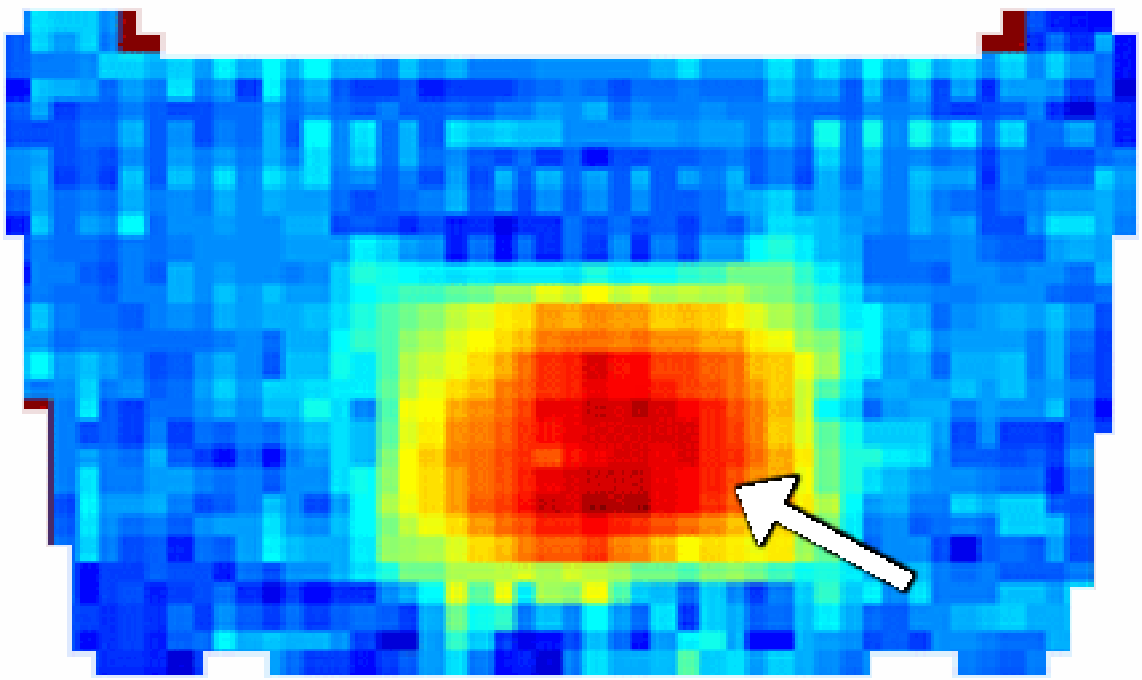

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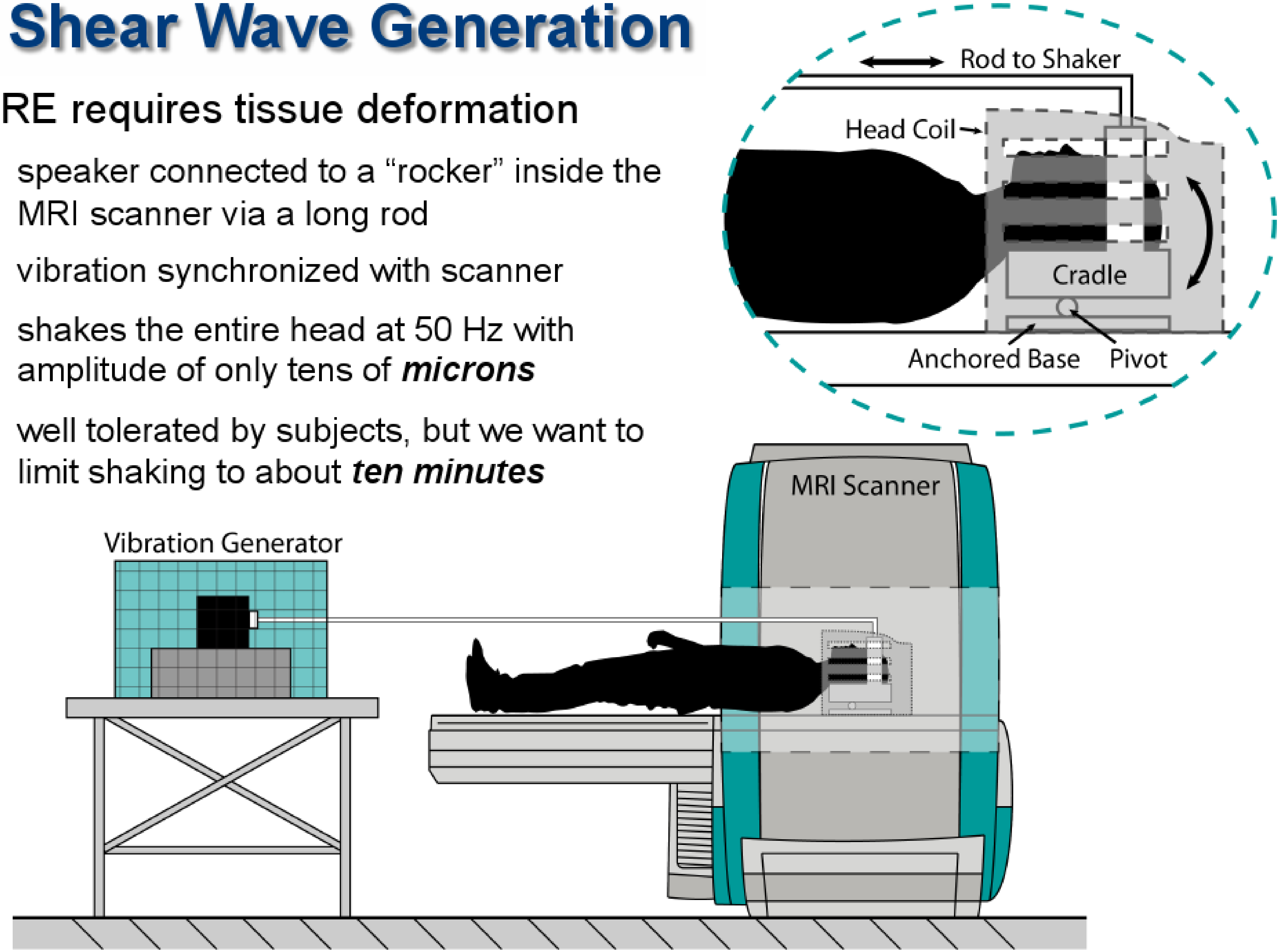
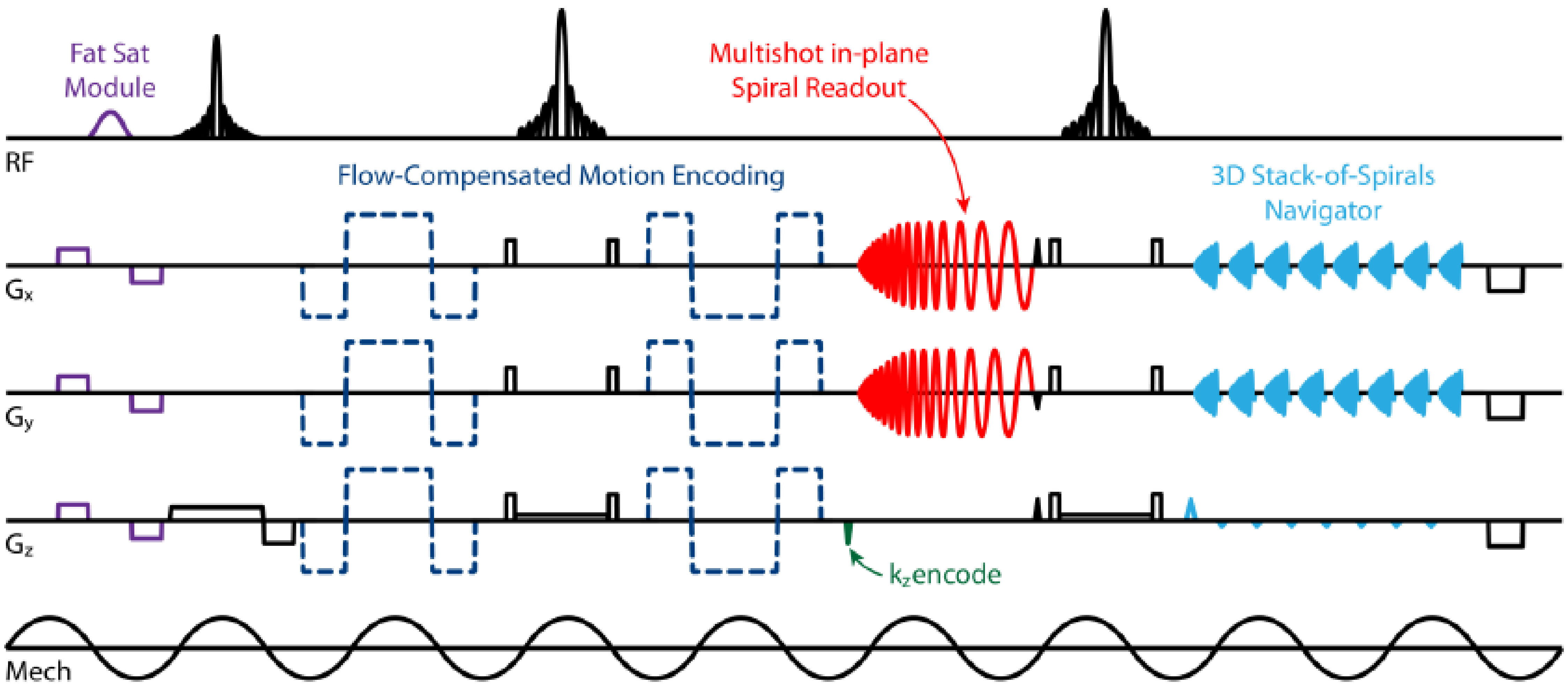


Imaging Challenges for MRE

- Similar to diffusion acquisitions: Need for high resolution and motion-induced phase error correction
- Also like diffusion imaging: MRE is a low SNR technique
  - Need short scan time, high resolution, multiple encoding directions, …
- High resolution and short acquisition time leads to long readouts
  - High magnetic susceptibility effects
- MRE must balance these to maintain short acquisition times, low sensitivity to susceptibility, and high SNR

Johnson, Holtrop, et al, *ISMRM*, 2013

3D Multislab, Multishot Sequence

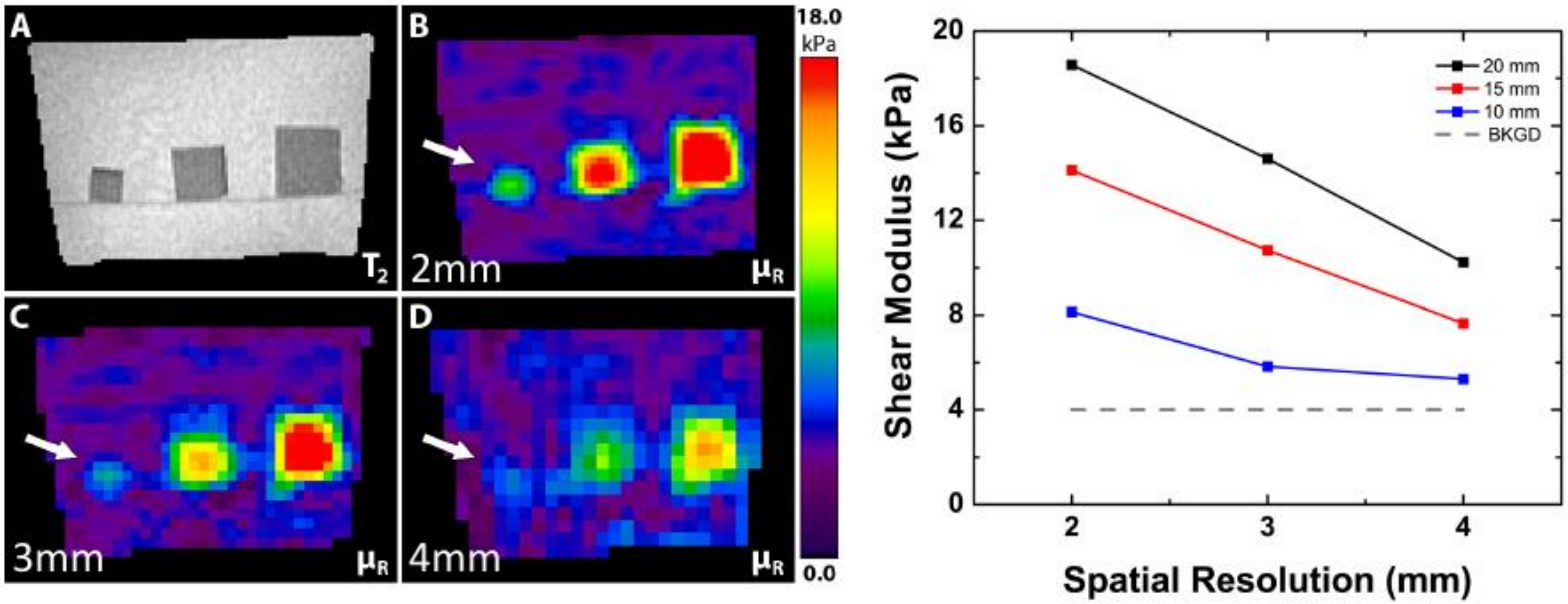


- 3D stack-of-spirals: 10 slabs / 8 slices / 25% overlap = **120 mm coverage**
- TR/TE = 1800/73 ms (**high SNR efficiency**); 2 x 2 x 2 mm^3 resolution
- 3D navigator after readout for correction of phase errors in k_x, k_y, and k_z
- ***Time Reduction***: parallel imaging (***R* = 3**) and only 4 MRE time points = **6 min total**
- Iterative reconstruction w/ motion correction, field correction, and SENSE on **GPUs using IMPATIENT code**

Johnson, et al, *Magn Reson Med*, in press

Need for Spatial Resolution

Problem: ***poor spatial resolution limits local quantitative accuracy***



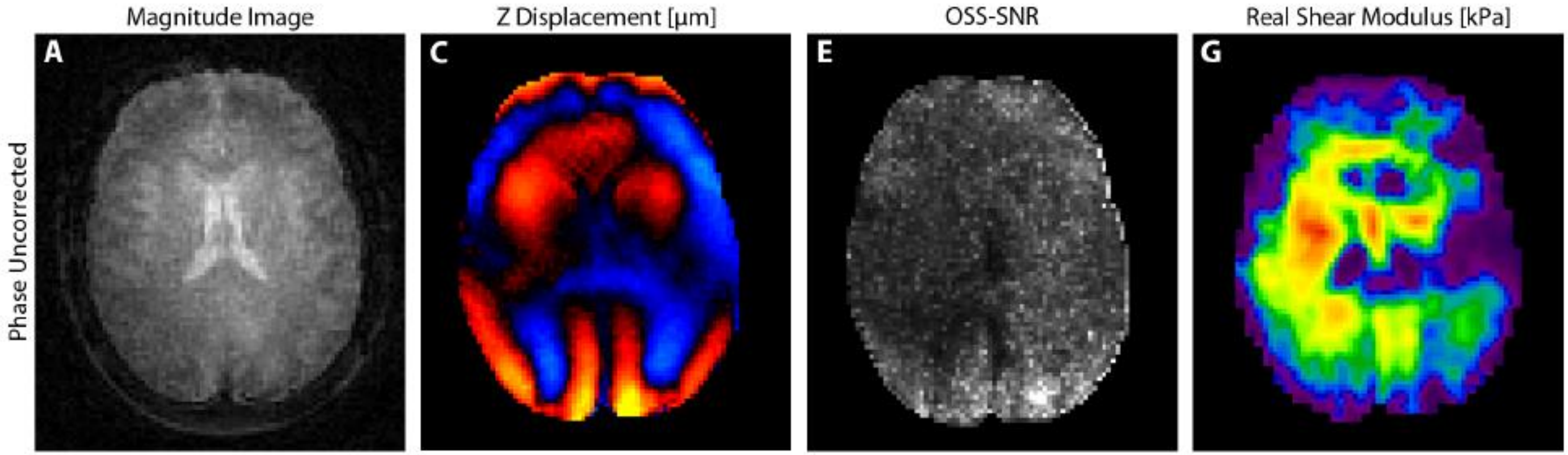
Most brain MRE studies use low spatial resolution and get only ***global*** values

Local estimates may improve ***specificity*** and ***sensitivity*** of MRE measures

- better distinguish early onset of disease
- aid in differential diagnosis (e.g. AD vs. NPH)
- monitor disease progression or response to treatment

Johnson, et al, *Magn Reson Med*, in press

Motion-Induced Phase Errors

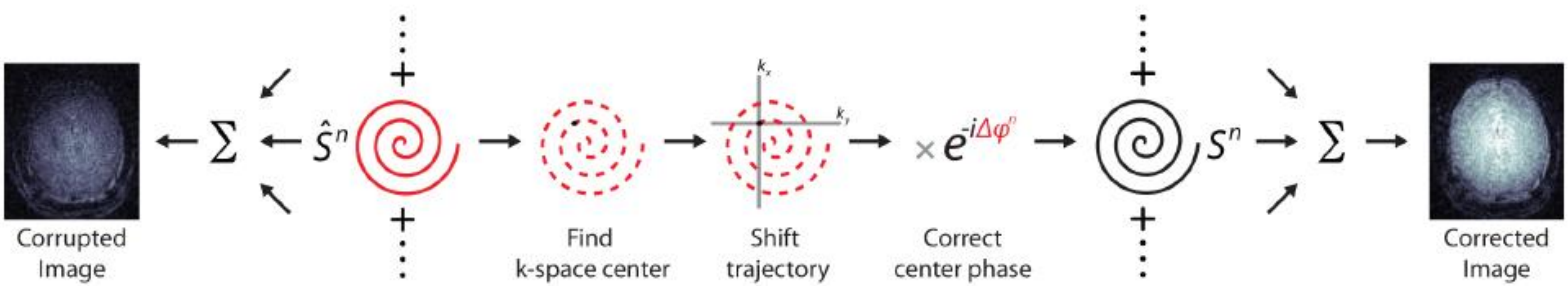


Errors occur in multishot imaging when the phase differs between shots

- leads to ***signal loss*** from cancellation and ***phase artifacts***

Correction requires navigator: self-navigation from oversampled center

- rigid body motion: translations (***phase offset***) and rotations (***phase ramp***; *k* shift)



Johnson, et al, *Magn Reson Med*, in press

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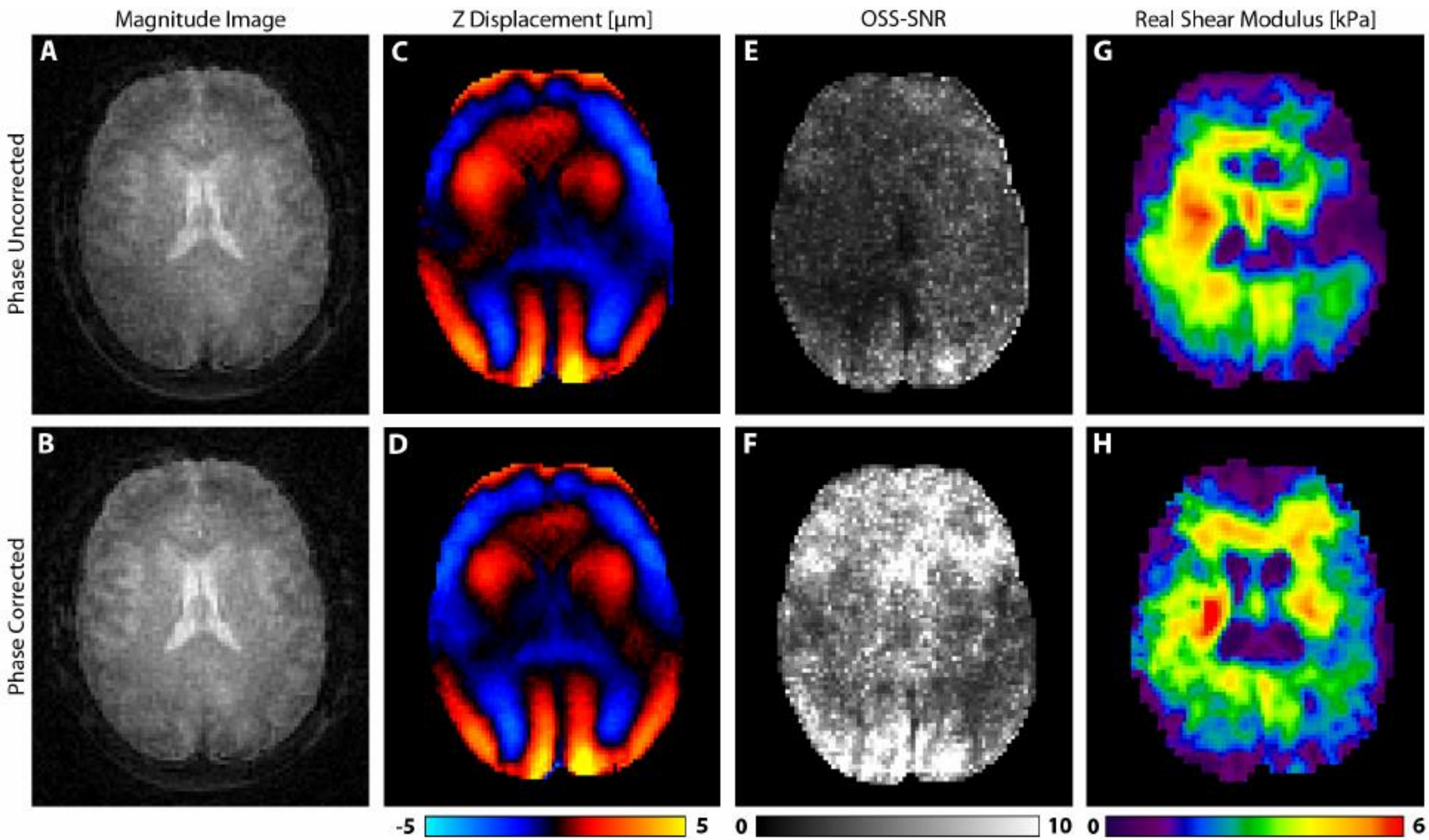
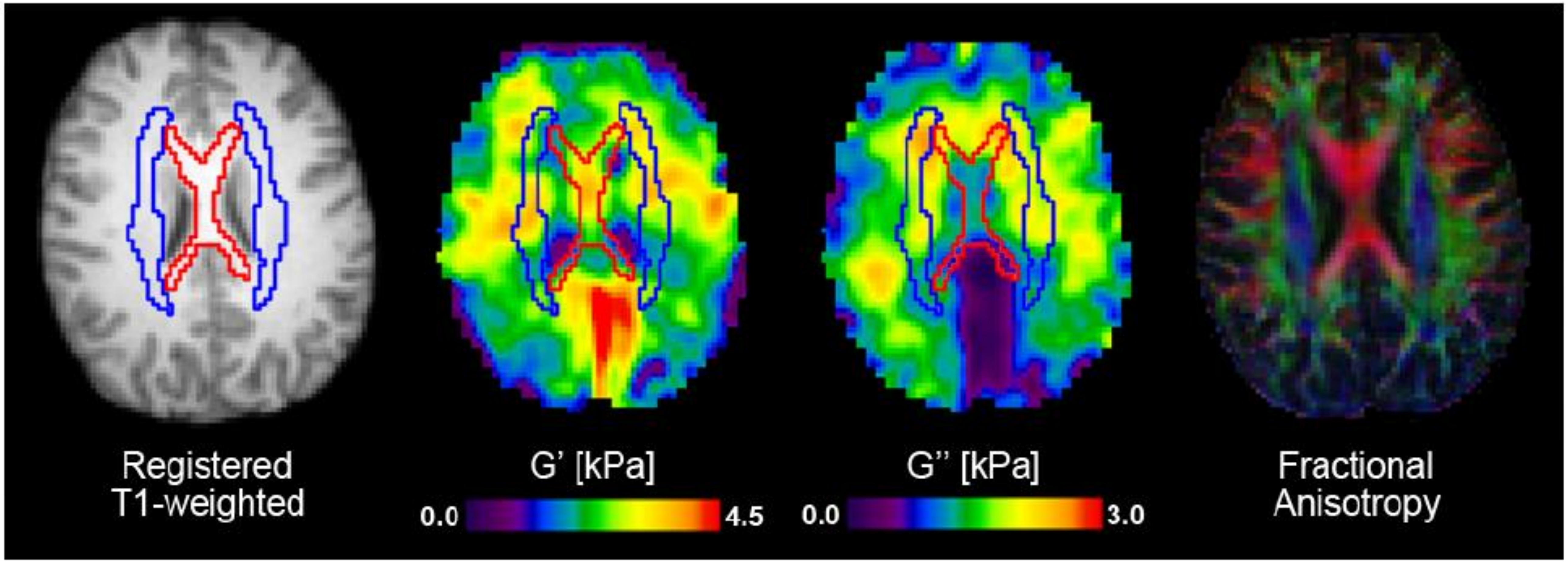


Phase error correction ***increases SNR*** and ***significantly improves*** property maps

Johnson, et al, *NeuroImage*, 2013

Delineating Anatomical Features in MRE

Objective: *provide reliable local mechanical property measures*



Mechanical property maps show anatomical features:

- Lateral ventricles (soft)
- Gray matter (soft)
- White matter tracts (stiff)

Quantify and compare both ***global*** and ***local*** regions:

- gray matter (**GM**)
- white matter (**WM**)
- corpus callosum (**CC**)
- corona radiata (**CR**)

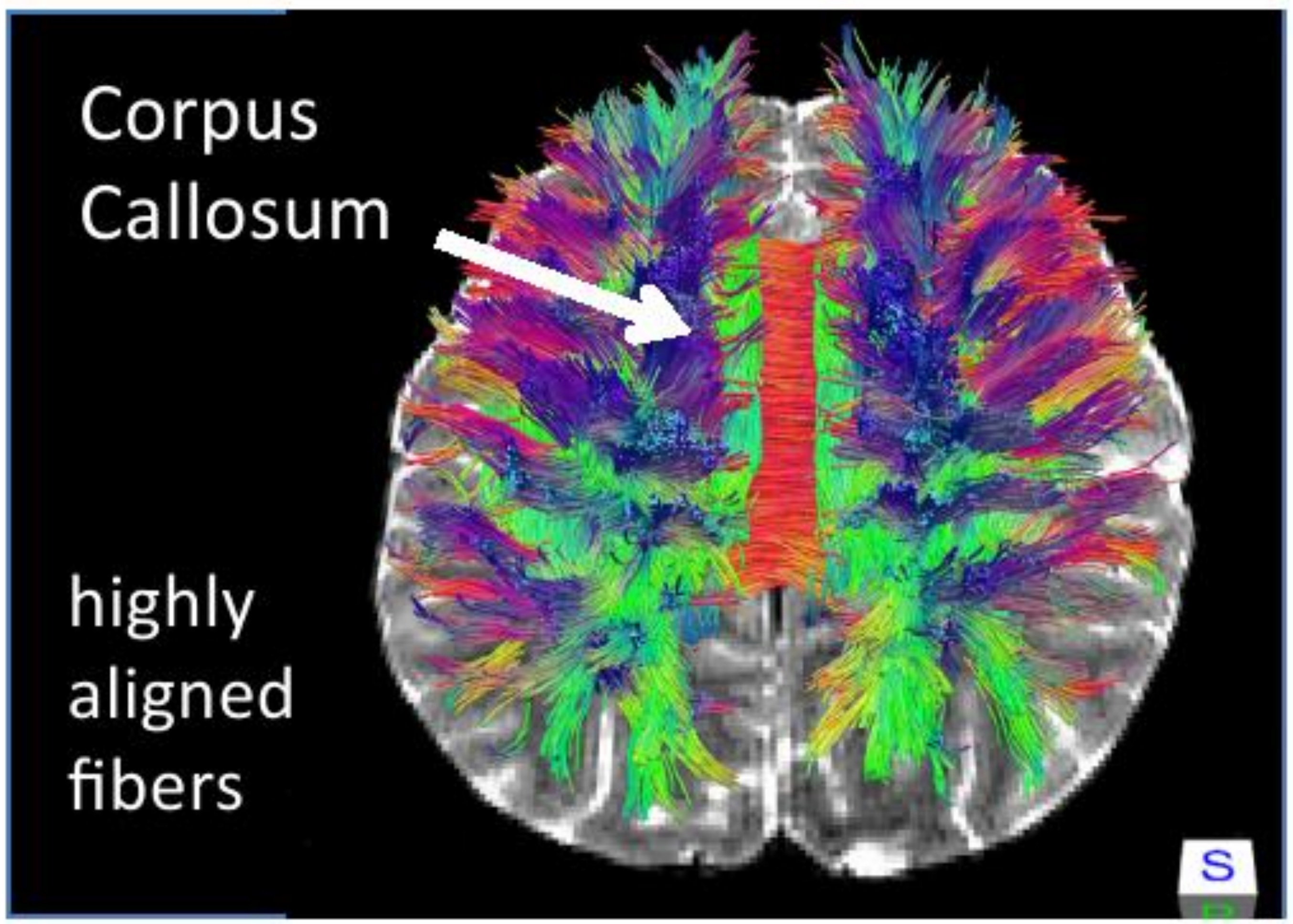
Johnson, et al, *NeuroImage*, 2013

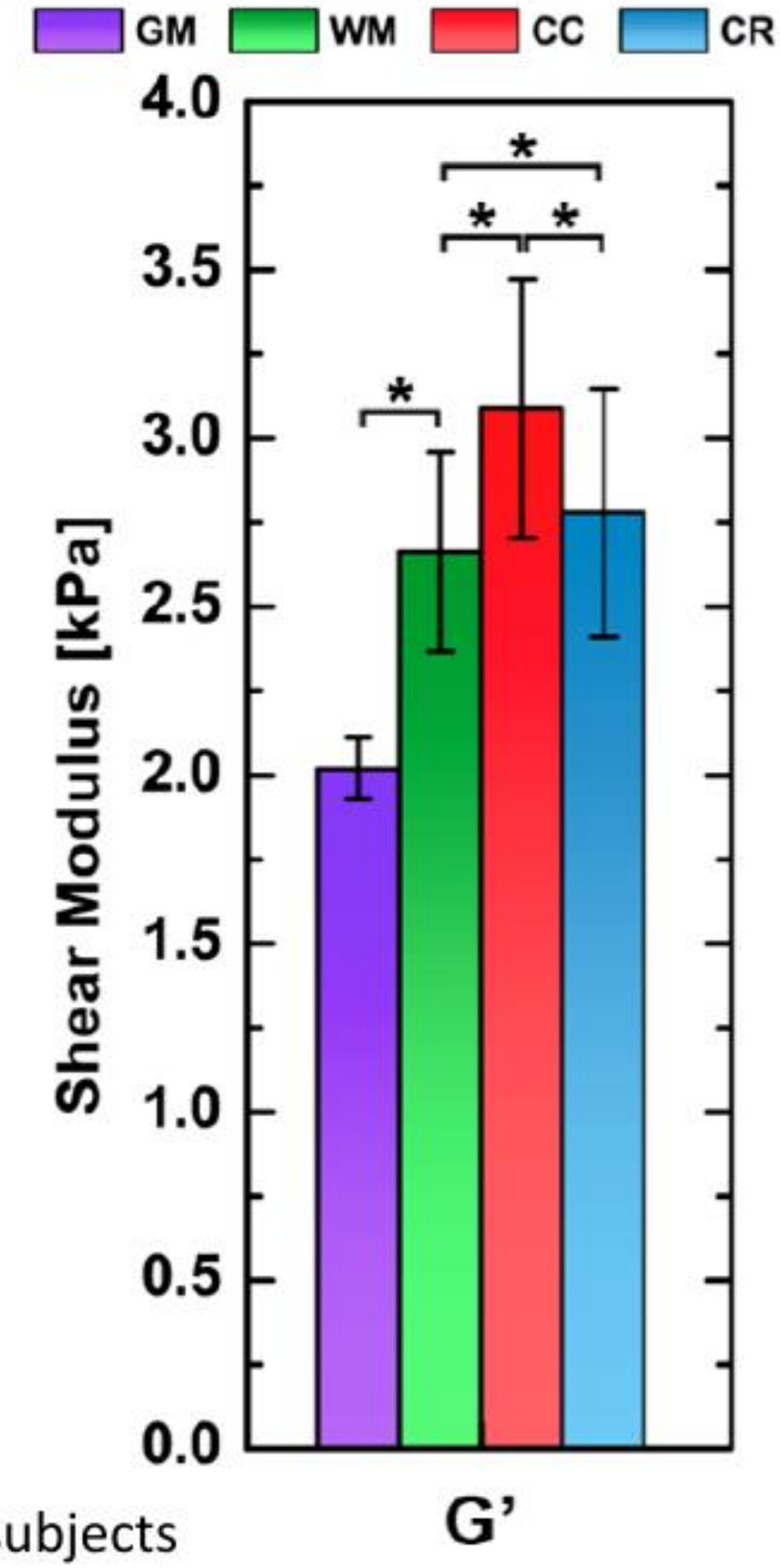
Difference in Storage Modulus (G')

G' is the storage modulus and describes tissue ***stiffness***

CC > CR > WM

- Axon properties and organization determine storage modulus
- High alignment of axons leads to higher stiffness





7 subjects

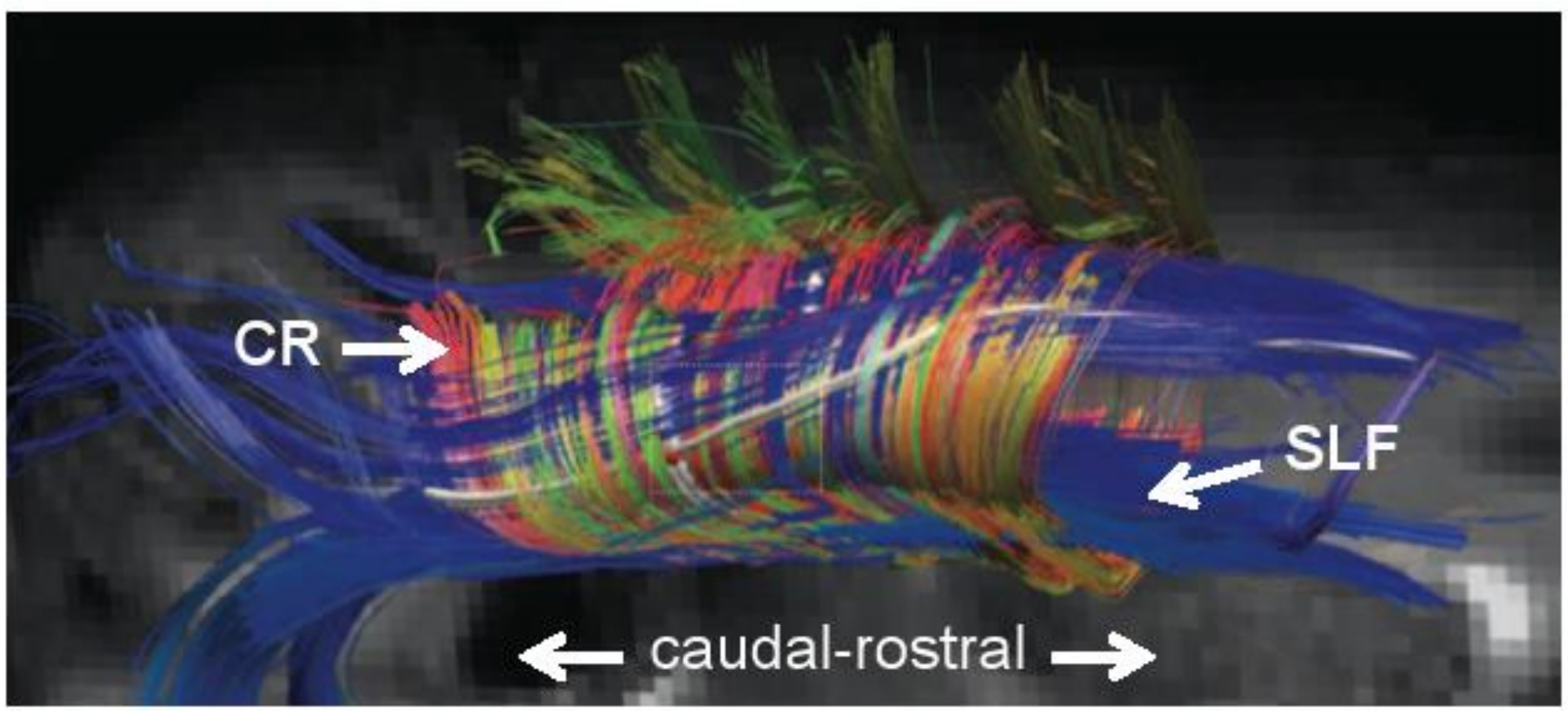
Johnson, et al, *NeuroImage*, 2013

Difference in Loss Modulus (G")

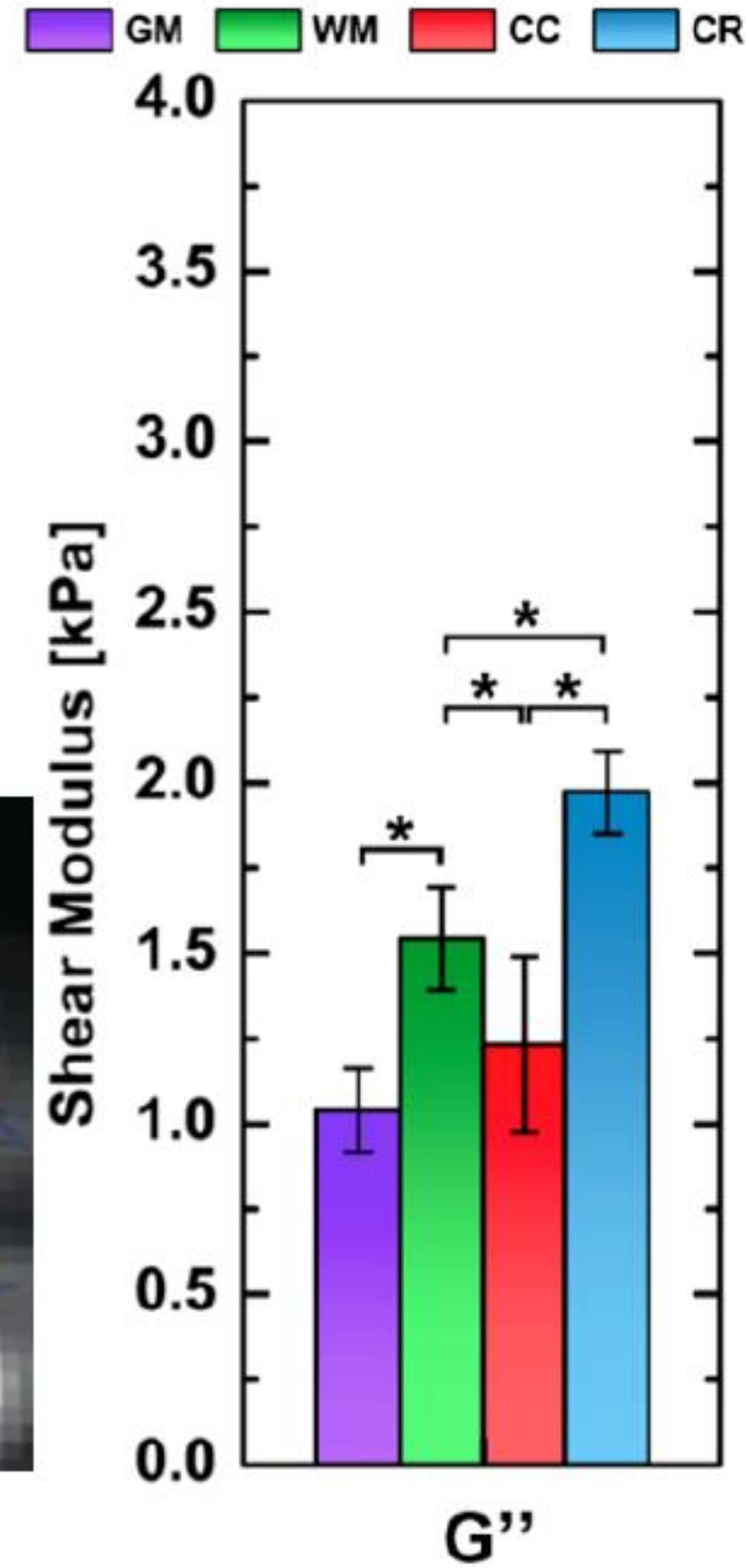
G" is the loss modulus and describes tissue ***viscosity***

CR > WM > CC

- Higher organization of glial matrix leads to higher viscosity
- G" may reflect crossing fibers of the CR; no crossings in the CC

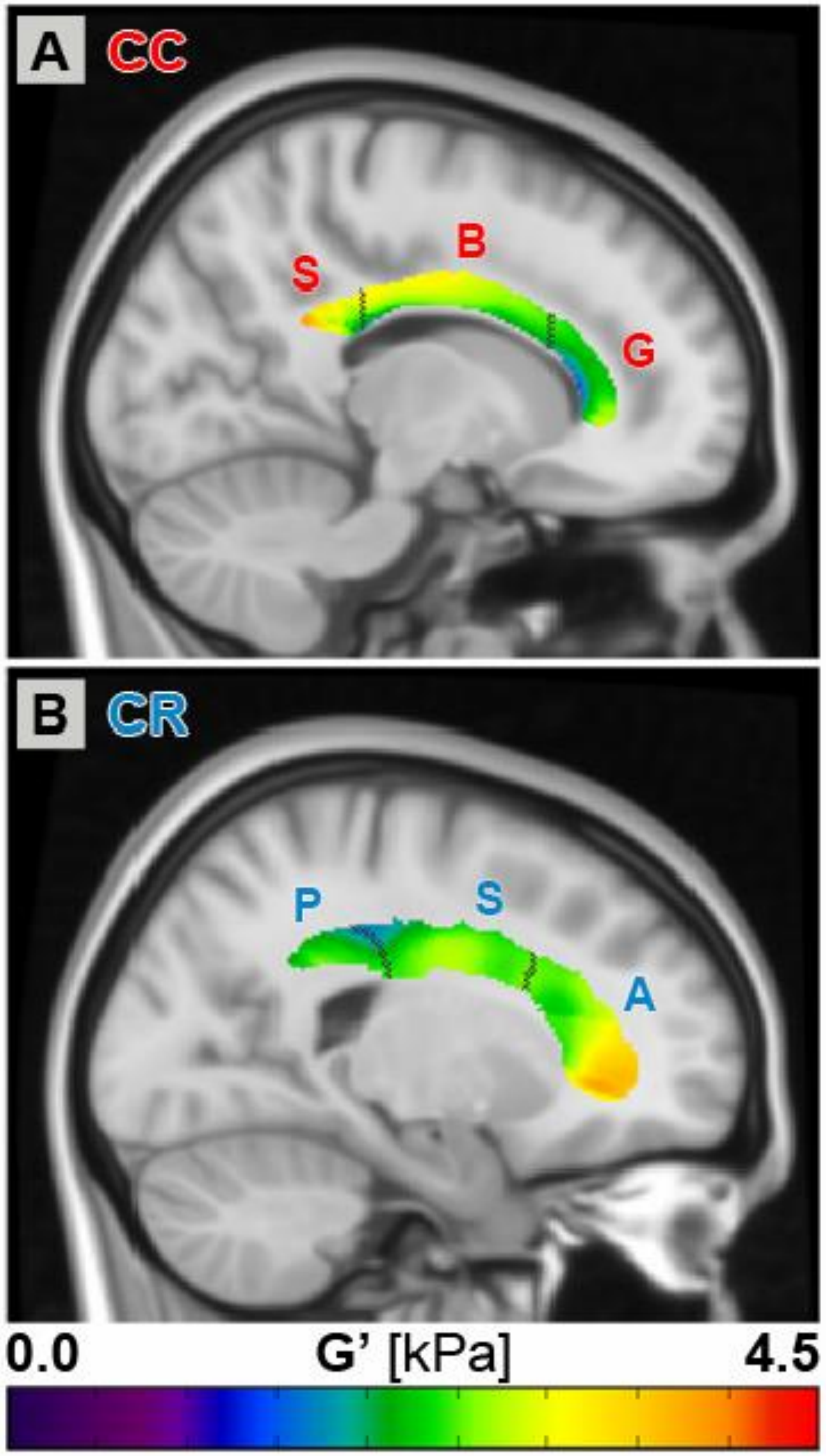


Wedeen, et al, *Science*, 2012



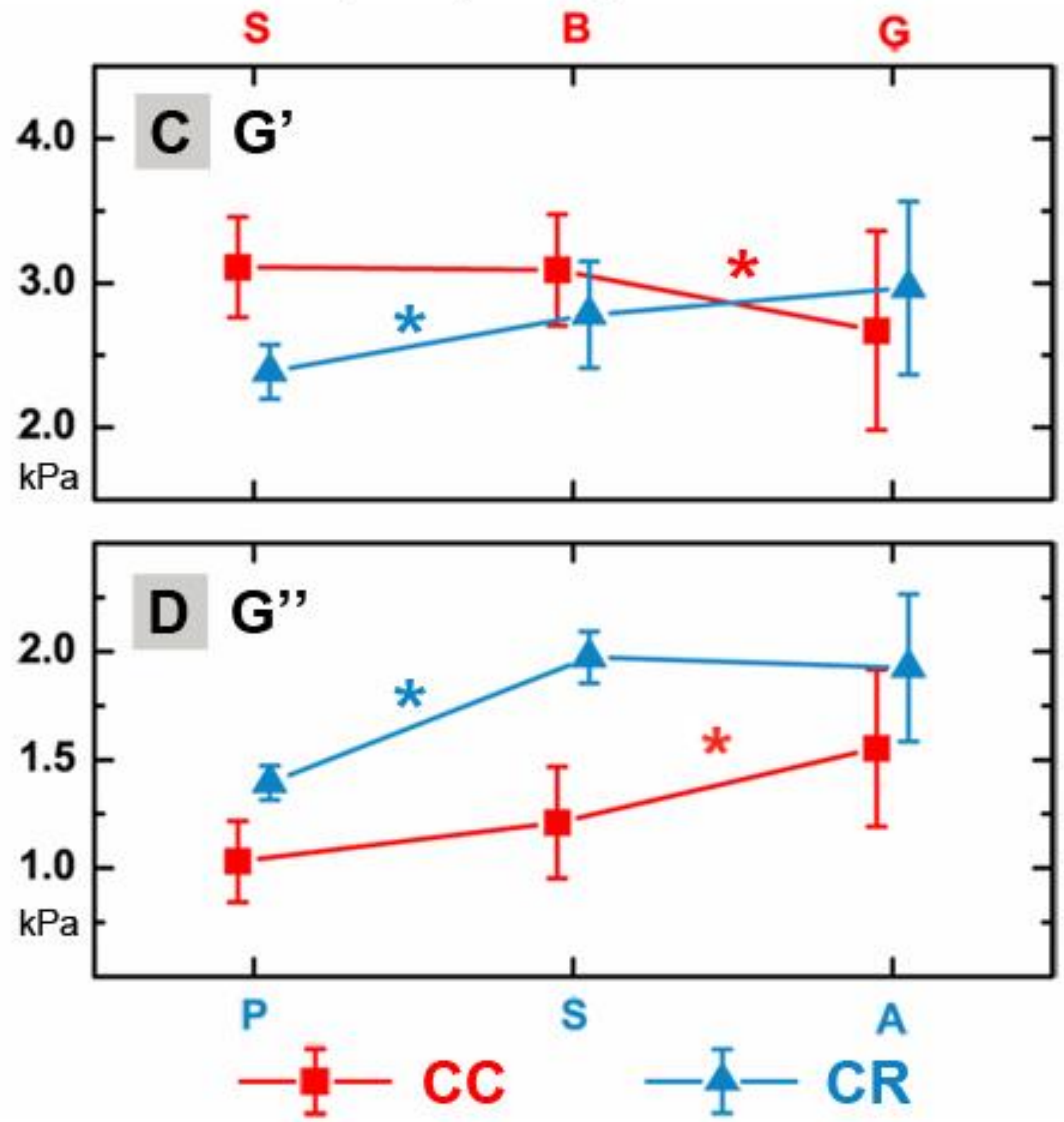
Johnson, et al, *NeuroImage*, 2013

Intra-Structure Property Heterogeneity



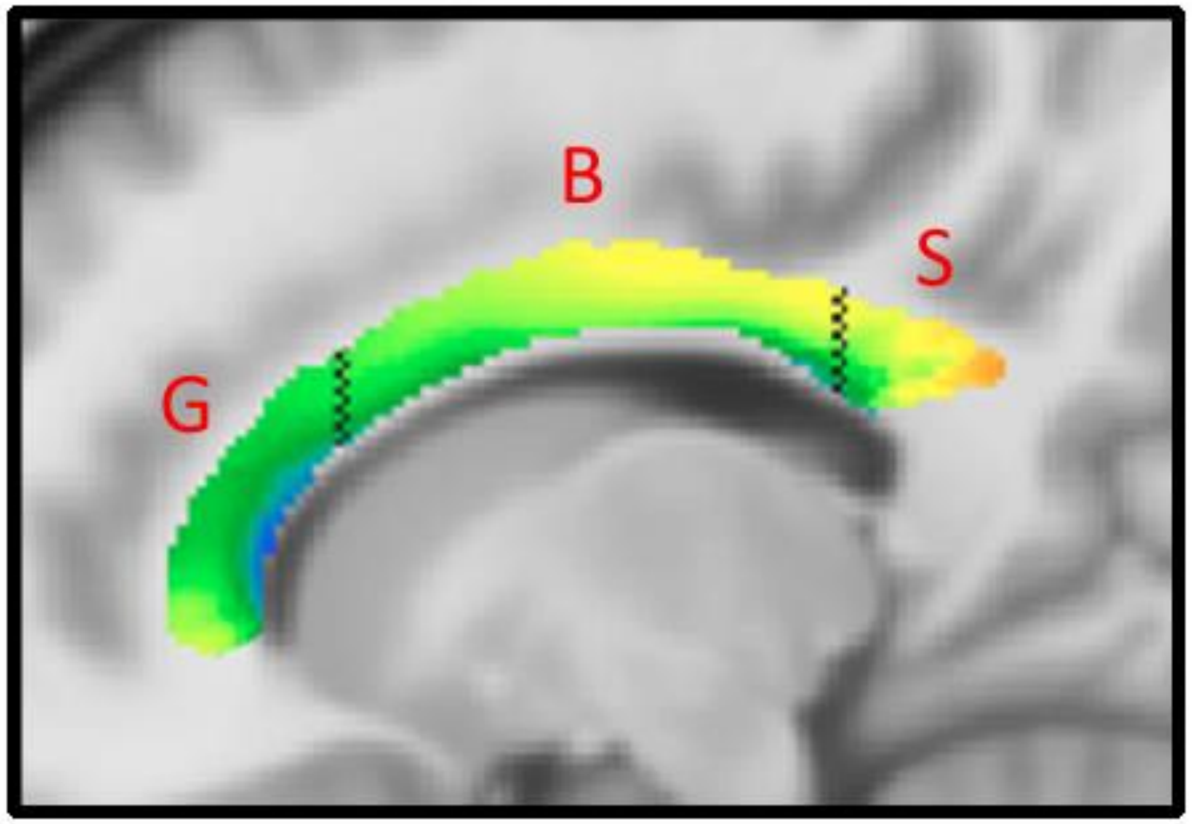
Three segments for both the CC and CR:

- **CC:** Splenium, Body, Genu
- **CR:** Posterior, Superior, Anterior

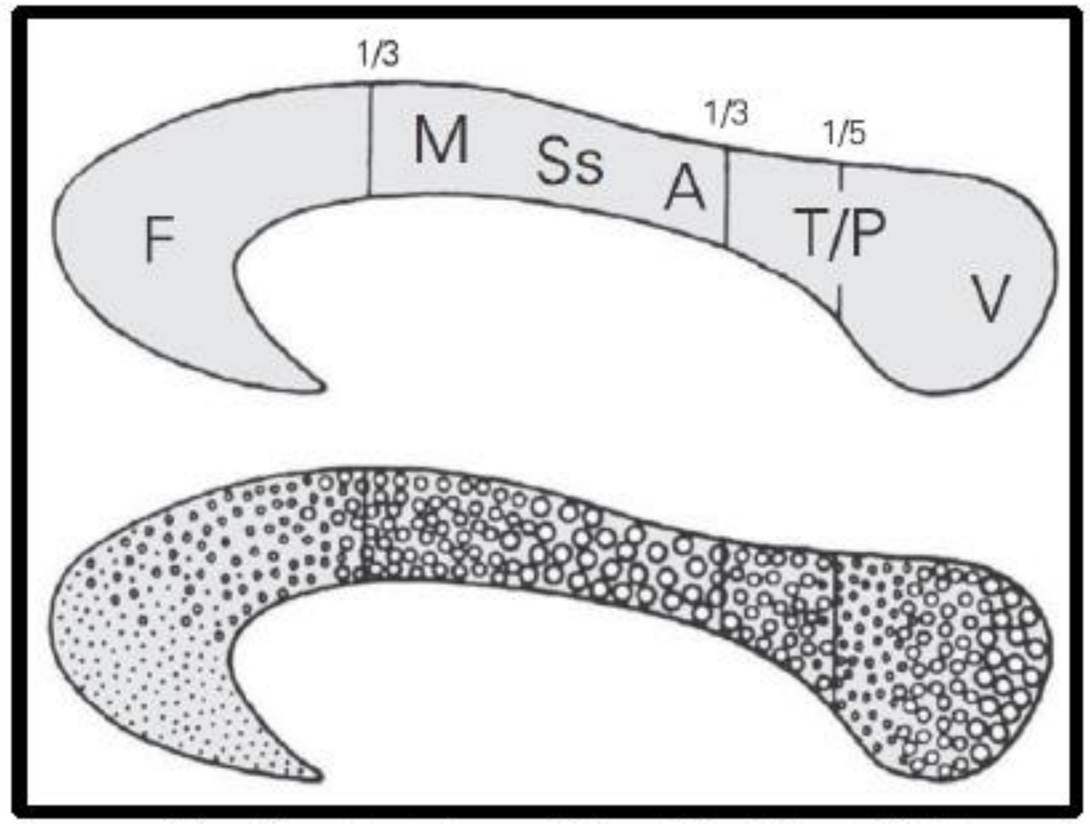


MRE properties reflect tissue ***microstructure***

Corpus Callosum Microstructure



Johnson, et al, *NeuroImage*, 2013



Aboitiz, et al, *Braz J Med Biol Res*, 2003

Body: motor, somatosensory, and auditory pathways

- large, highly myelinated axons for fast transmission **→ high G'**

Genu: frontal pathways

- small, poorly myelinated axons; high axon density **→ high G"**

Splenium: temporoparietal and visual pathways

- mix of both large (V) and small (T/P) axons

LaMantia, et al, *J Comp Neurol*, 1990; Aboitiz, et al, *Bain Res*, 1992; Aboitiz, et al, *Braz J Med Biol Res*, 2003

Johnson, et al, *NeuroImage*, 2013

Corpus Callosum: MRE / DTI

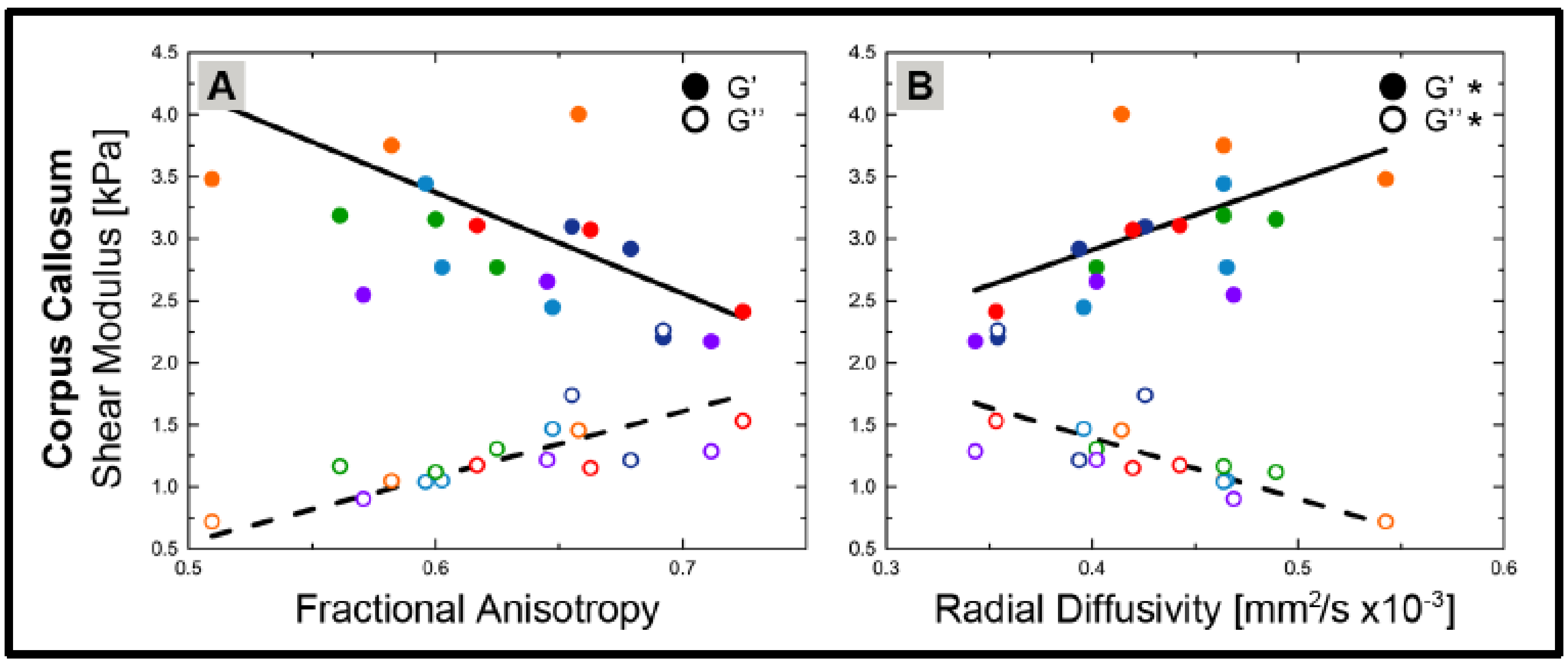
Do DTI measures correlate with differences in MRE measures ***within the CC***?

YES: MRE (G' and G'') correlated with DTI (FA and RD) – ANCOVA

- Both G' and G'' correlate with RD ($p < 0.05$)
- Correlations with FA have only trend-level significance ($p < 0.10$)

This is a reflection of axon diameter in different segments of the CC

- Larger axons exhibit higher RD and lower FA [Barazany, et al, *Brain*, 2009]
- Therefore, larger axons → ***higher G'*** and ***lower G''*** (fewer glial connections)



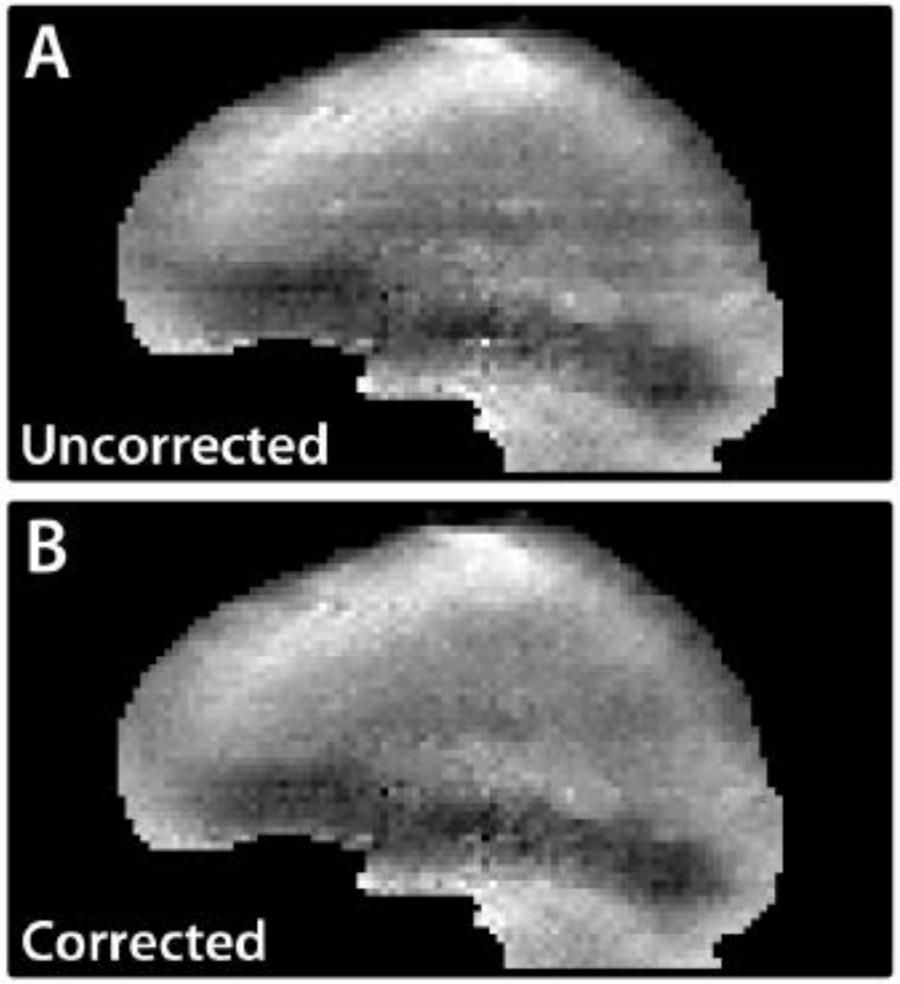
Johnson, Holtrop, et al, *ISMRM*, 2013

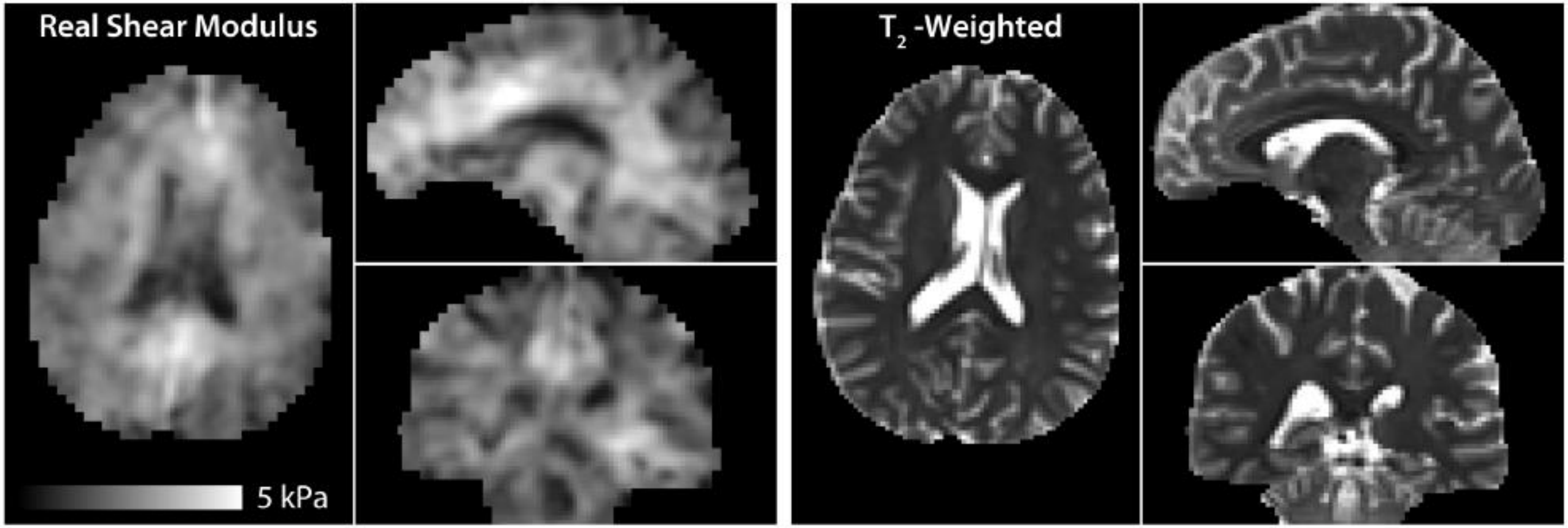
Whole-Brain, High-Res MRE

Phase error correction ***recovers SNR*** and removes ***slab-to-slab inconsistencies***

Shear modulus agrees well with anatomy

- Excellent definition on lateral and fourth ventricles and cortical sulci
- Cerebellum is soft, as previously reported
- Brainstem appears stiff; expected given its structure



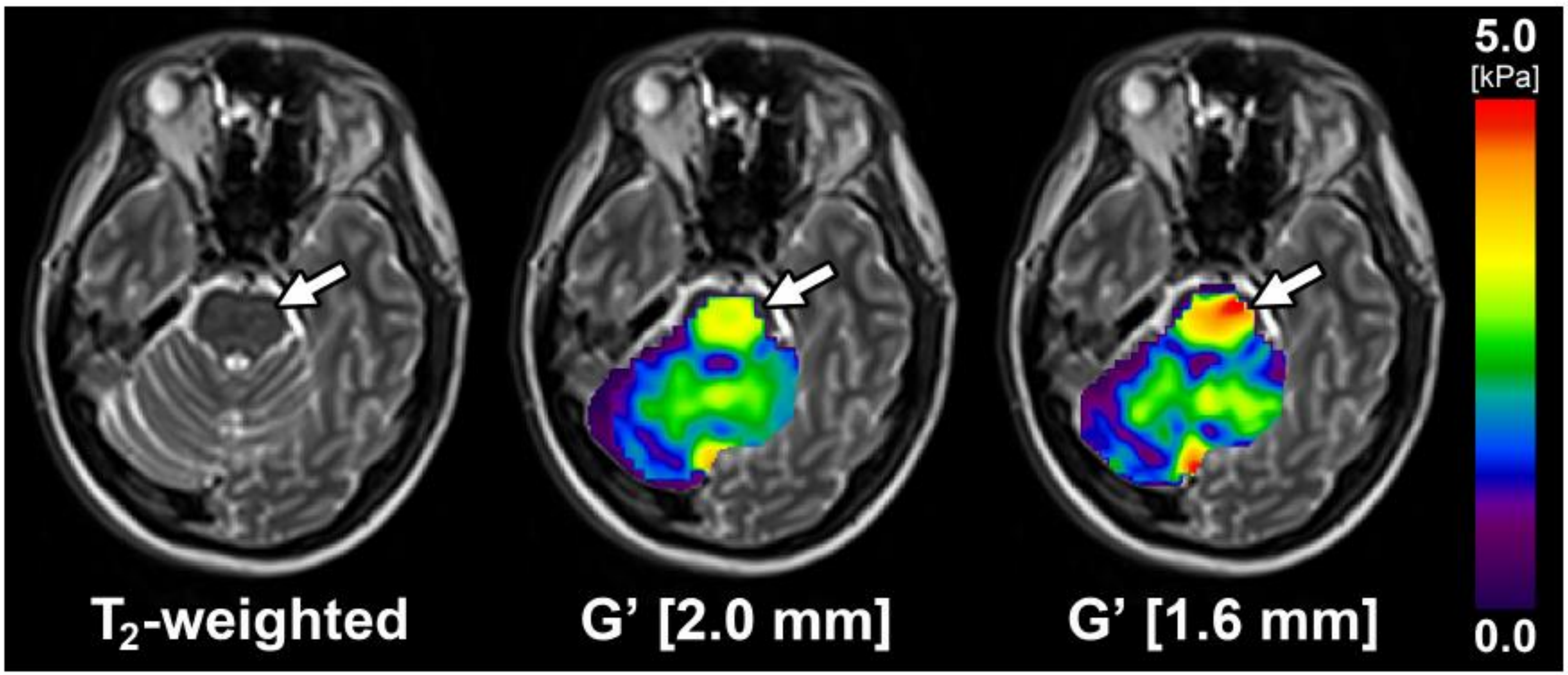


Johnson, Holtrop, et al, *ISMRM*, 2013

Pushing to Higher Resolution

Acquired dataset with 1.6 mm isotropic resolution

- OSS-SNR: ***3.07***; total acquisition time: ***11 min 45 s***
- Same subject scanned as with the 2 mm acquisition; results co-registered
- Brainstem *G'* estimates: 2.0 mm = **3.01 kPa**; 1.6 mm: ***3.57* kPa!**
- Small, very stiff structure needs the higher-resolution acquisition for accuracy



Conclusions

MRI provides many views into brain physiology, organization, and structure.

By developing methods to improve the spatial resolution achievable with the specialized acquisitions of diffusion weighted imaging and magnetic resonance elastography, we are able to determine complementary architecture information:

- DTI reflects information on orientation of axons and membrane integrity for restrictions of diffusion
- MRE provides information on axonal neighborhood and presence of intersecting fiber bundles. Also reflects degradation of interactions between axons and extracellular matrix.

These techniques will enable sensitive measures of age- and disease-related changes to neuronal tissues

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