Measuring brain stiffness with MR Elastography

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Exciting time to be doing MRI at Illinois

- 2 state-of-the art 3 T human MRI Prisma systems, one multinuclear
- New 9.4 T, 30-cm animal MRI system coming next year
- MRI on the rise in town: Vet Med 3 T Skyra, New 3 T Skyra at Christie (March 2019)
- Carle – new imaging center of excellence
  - People, equipment, and collaboration
BIC traces its roots to the Biomedical Magnetic Resonance Lab, founded by Paul Lauterbur:

- Professor at UIUC, 1985-2007
- Winner of the Nobel Prize for the invention of MRI in 2003

2003 Nobel Prize in Physiology or Medicine for invention of magnetic resonance imaging

Shared Nobel Prize with Peter Mansfield – was a post-doc at Illinois in 1962
1974 - Lauterbur first human MRI scanner found August 2017

Also - 1976!
What my group does: Design new ways to measure physiology with MRI

Carrier Phrase – “I said writing to you, I said riding to you”

M. Barlaz et al, InterSpeech, 2015.
Objectives of this Talk

• Talk about the basics of using MRI to non-invasively measure brain mechanical properties: MR elastography (MRE)
• Give an overview of the applications of MRE
• Talk about my experience with the IRB at UIUC and Carle
MRE Team

- Aaron Anderson, PhD Beckman-Carle
- Hillary Schwarb, PhD BIC/IHSI
- Tracey Wszalek, PhD BIC
- Alex Cerjanic, MS Bioengineering
- Graham Huesmann, MD PhD Carle
- Neal Cohen, PhD Psychology
- Aron Barbey, PhD Psychology

- Curtis Johnson – U. of Delaware
- Keith Paulsen, Matt McGarry - Dartmouth
- Elijah Van Houten – Université de Sherbrooke
- Ken Aronson – Carle Foundation Hospital
- Ana Daugherty – Wayne State University
The problem for every imager: Not enough SNR

Interesting contrasts available with MRI
- Diffusion Imaging – showing restrictions to diffusion in the brain – such as fiber pathways
- Magnetic Resonance Elastography - measuring mechanical properties as we “gently vibrate” the brain

However
- Currently low spatial resolution
- Always SNR starved
- As spatial resolution increases, SNR decreases
  (cubic relationship!)

Underlying image from Augustinack, 2010
Balancing act: coverage versus resolution versus SNR...

2D imaging with lots of slices
- very little increase in SNR as TR > T₁

3D imaging of full volume
- excitations per volume increase SNR
- need a very short TR for OK scan time

Multiple 3D volumes (slabs)
- fewer volumes to excite keeps TR short
- multiple excitations per slab for SNR
- optimal SNR efficiency

SNR increase by factor of 2-4
For FREE at the scanner
Cost is computation later
Complications of real experiment

- Subject movements
- Cardiac pulsation
- Dependent on diffusion encoding

Magnetic Field Inhomogeneity

Motion-induced Phase

![Image of brain MRI with echo spacing 0.0 ms]

![Table showing full resolution navigators and correction effects]
Challenges addressed through acquisition, reconstruction, and computational approaches

- 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
Enabling Unprecedented Signal and Resolution

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

- 0.8 mm isotropic DWI, b-value 1000 s/mm²
- 0.512 μL voxel volume

Fine fiber features are accessible to interrogate for neuronal integrity measures.
Improved delineation of fiber pathways

3D multi-shot, multi-slab navigated spiral DTI
- SNR efficient
- Correction for:
  - Motion induced phase
  - Magnetic field inhomogeneity
- CHALLENGE:
  - Acquisition Time
  - Computation!

Holtrop and Sutton, J Medical Imaging. 2016.
• Palpation is central to medicine
• MRE is “Quantitative Palpation”
  • Specific
  • Localized
  • Repeatable
  • Non-invasive
• Diagnosis & staging:
  • Liver diseases:
    • Chronic liver disease (fibrosis)
    • Non-alcoholic fatty liver disease
    • Hepatitis B & C
  • Replacing invasive biopsies
  • Focal (biopsy) → sampling problem
Why Mechanical Properties in the brain?

- May reflect tissue organization at micro-scale – how cells are packed and connected
  - axonal integrity / myelination
  - axonal packing / organization
  - Inflammation, synaptic density, …

- Potentially larger dynamic range than other forms of imaging

- Demonstrated decrease in stiffness with neurodegeneration

Mariappan, et al., Clin Anat, 2010
How does MRE work?

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

Typical MRE experiment:
- shear deformation with external actuator
- phase contrast imaging of shear waves
- inversion algorithm for property estimation
Measuring Structural Integrity of the Brain: (MRE)

MRE measures mechanical properties by vibrating tissue

- Vibrations applied via speaker/rocker or subwoofer/pillow
- vibration synchronized with scanner
- shakes the entire head at 50 Hz with amplitude of only tens of microns
Pulse sequence: Encoding Small Displacements

- 50 Hz excitation
- 2x2x2 [mm$^3$] or smaller
  - full brain coverage
- 6 min (clinically relevant)
- 3D complex displacement field
- Displacements 10 μm

High-Resolution Brain MRE

Multishot spiral acquisition: **whole brain coverage at up to 1.25 mm isotropic resolution**
- 3D, full-vector shear displacement fields in the brain in < 10 min.
- High SNR for estimating mechanical properties through inversion


Head / Foot

Anterior / Posterior

Left / Right

Displacement [µm]
Mechanical property maps show anatomical features:
- Lateral ventricles (soft)
- Gray matter (soft)
- White matter tracts (stiff)

Can quantify and compare both **global** and **local** regions:
- gray matter (GM)
- white matter (WM)
- corpus callosum (CC)
- corona radiata (CR)

A major limitation to previous applications of MRE has been insufficient resolution.

Sack et al. (2011) *J Neuro Methods*

Johnson et al. (2016) *HBM*
Hippocampal viscoelasticity and relational memory

Hippocampal viscoelasticity is strongly related to relational memory performance. Elastography provides sensitive measures of tissue integrity and health.

*Adjusted Damping Ratio = 1 - Damping Ratio
• Dissociation of structure-function relationships characterized by MRE
• Hippocampal viscoelasticity was related to relational memory, but not fluid intelligence
• Orbitofrontal cortex viscoelasticity was related to fluid intelligence, but not relational memory

Johnson et al. (2018) NeuroImage

*Adjusted Damping Ratio = 1 - Damping Ratio
Hippocampal Viscoelasticity, Fitness, & Relational Memory

Schwarb et al. (2017) NeuroImage
• Viscoelasticity differs between subfields
• CA3/DG viscoelasticity is related to relational memory performance
Longitudinal Studies: Can we change stiffness?

- Small scale study in MS
- 8 subjects
- 12-week progressive treadmill walking exercise training
- Large intervention effect: hippocampal $\mu$ (d = 0.94) and hippocampal $\xi$ (d = −1.20)

Clinical Applications: Mesial Temporal Lobe Epilepsy

- Hemispheric asymmetries in shear stiffness differentiates patients from controls with high accuracy
- Use for pre-surgical assessment for epilepsy patients through our collaboration with Carle

Johnson et al. (in preparation)
Further Technical Advances Leading to Higher Resolution MRE

3D Multiband, Multishot Spiral MRE Sequence

Multishot Stack-of-Spirals

Spiral-In 3D Navigator
Multi-band MRE

No Correction

Nonlinear Correction

2.0 mm time = 2:53
1.6 mm time = 4:19
1.25 mm time = 5:46

OSS-SNR 8.50
OSS-SNR 5.35
OSS-SNR 3.26
Conclusion

- MRE enables a quantitative measure of tissue status
  - Reproducible
  - Quantitative characterization of tissue mechanical properties
  - Specifically correlated with functional status
  - Sensitive to pathological changes, aging, and even healthy performance
- Further advances are enabling higher spatial resolution
- High sensitivity: we are finding highly significant relationships
IRB Challenges

• Our work spans multiple institutions, often as an exchange of technology
• Work with Carle is collaborative
  • Recruitment of patient populations to scan at Beckman, potentially with OSF and other collaborators/community
  • Some studies run at Carle with Carle patients
  • Intellectual contributions from Dr.’s Huesmann, Olivero, Huston, Biswas
• New requirements have required significantly more time than previously
  • Recruitment of patients from Carle - our UIUC IRB underwent full review at Carle – 5 months for approval
• These are growing pains and need to be streamlined
• Communication lines are not clear due to procedural differences
More challenges ahead

• New requirements on students/researchers accessing Carle space
• Integration of MRI research with Carle with new MRI machines
• Challenges are across the board (i.e. not just Carle)
  • New human subjects requirements in grant applications
  • Single IRB requirements from NIH, even if not clinical trial
  • Push for more things to be called clinical trial

• Advice: Get involved and educated. Leverage the strength and size of research at UIUC
• Served on the IRB from 2012-2015.
• **MRFIL**: Aaron Anderson, Alex Cerjanic, Meltem Uyanik, Natalie Aw, Steve Peng

• Curtis Johnson, Joe Holtrop, Giang-Chau Ngo, Anh Van, Dimitrios Karampinos, Maojing Fu

• Tracey Wszalek

• Graham Huessman, Jason Huston (Carle)

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http://mrfil.bioen.illinois.edu