Introduction to Multimodal Neuroimaging
Structure I: T1, T2, ultra-high field

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Outline

- Overview of structural MRI research   Howard

- Review of Key MRI Pulse Sequences Maria

- Machine learning Model of Brain Aging Maria

- Ultra High Field (7T) MR Imaging   Howard

MRI Key Concepts

Human Subject Issues
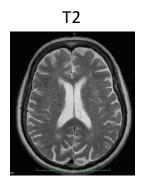- No radiation exposure (unlike xray, PET, CT),
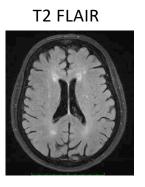- thus multiple scans possible

Risks:
- Loud
- Tight space: concern about claustrophobia & participant size
- Metal in/on body can heat, move, or cause artifact
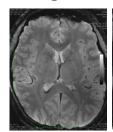
MR Imaging Key Concepts (Cont)

- Detect signal from ^1H of H_2O

- In conventional imaging, signal intensity (greyscale) is related to MR relaxation properties of ^1H_2O such as T1 or T2 relaxation times.

- Water in grey matter has different T1 and T2 relaxation times than water in white matter or CSF. (These are standard structural sequences).

- Some standard sequences (T1, T2, SWI) are discussed today.

- Others include, BOLD fMRI, ASL, DTI, …

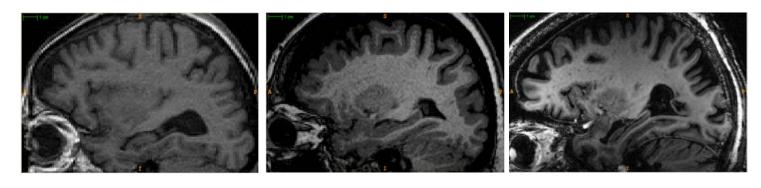T1   T2   T2 FLAIR   Ultra-High Field (7T) Susceptibility Weighted Imaging

MRI Modalities:

- T1-Weighted ('Anatomic')
  - Morphometry: regional volumetrics, cortical thickness, shape

- T2-Weighted (with or without FLAIR)
  - WMH, lacunes

- SWI (Susceptibility weighted Imaging)
  - Microbleeds, perivascular spaces, vessels, anatomic landmarks

T1-Weighted Anatomic Scans

- Weighted towards imaging differences in T1 (longitudinal) relaxation properties of tissue.

- Short TR, short TE,

- Accentuates gray/white contrast

- Often Volumetric High resolution, scan such as SPGR, MPRAGE is used

| 1.5 Tesla | 3 Tesla | 7 Tesla |

Automated Morphometry

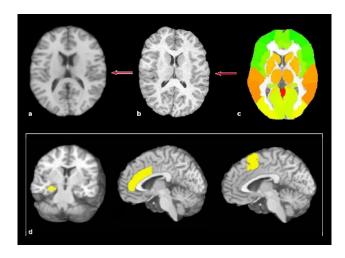All rely to some extent on basic image processing functions of
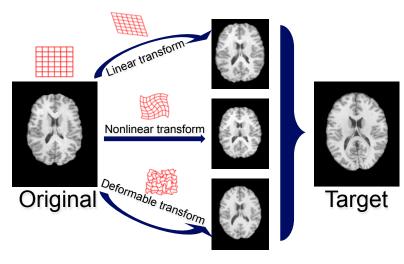**Registration** (pair-wise): align one image to another
Segmentation: label voxels which meet a criteria

- Atlas-Based Segmentation
- Voxel-Based Morphometry (VBM)
- Tensor-Based Morphometry (TBM)
- Cortical Thickness
- Shape Analyses

Automated Morphometry

- Atlas-Based Segmentation
  - Registering the atlas brain into the individual brain space.
  - Specific regions in the individual brains are then segmented using the computed spatial transformation and the MNI anatomical template.

Cross Registration

Automated Morphometry

- Atlas-Based Segmentation:

  template

  ↓

  individual

- Voxel-Based Morphometry (VBM)

- Tensor-Based Morphometry (TBM)

- Cortical Thickness

- Shape Analyses

All rely to some extent on basic image processing functions of
Registration (pair-wise): align one image to another
Segmentation: label voxels which meet a criteria

Automated Morphometry

template

- Atlas-Based Segmentation:

↓

individual

- Voxel-Based Morphometry (VBM):

individual

- Tensor-Based Morphometry (TBM):

↓

template

- Cortical Thickness

- Shape Analyses

All rely to some extent on basic image processing functions of
Registration (pair-wise): align one image to another
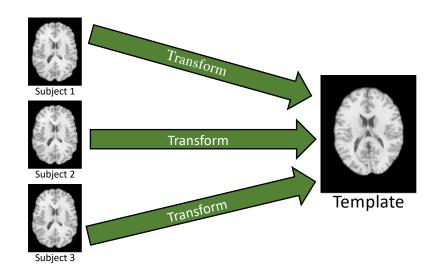**Segmentation**: label voxels which meet a criteria

Automated Morphometry

- Atlas-Based Segmentation:

template

↓

individual

- Voxel-Based Morphometry (VBM):

individual

- Tensor-Based Morphometry (TBM):

↓

template

Subject 1

Transform

Subject 2

Transform

Subject 3

Transform

Template

Automated Morphometry

- Atlas-Based Segmentation:

  template

  ↓

  individual

- Voxel-Based Morphometry (VBM):

  individual

  ↓

  template

- Tensor-Based Morphometry (TBM):

Automated Morphometry

- Atlas-Based Segmentation:

template
↓
individual
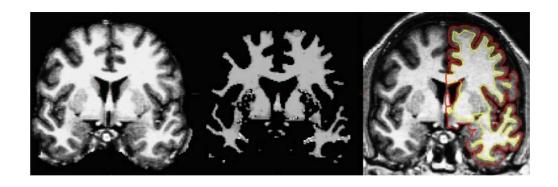
- Voxel-Based Morphometry (VBM):

individual
↓
template

- Tensor-Based Morphometry (TBM):
- Cortical Thickness
- Shape Analyses

Automated Morphometry

- Atlas-Based Segmentation:

- Voxel-Based Morphometry (VBM):
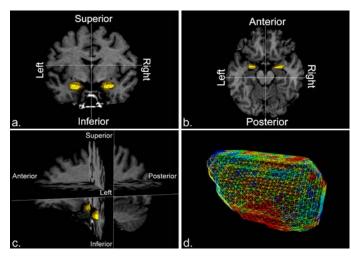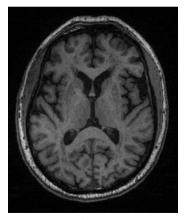- Tensor-Based Morphometry (TBM):
- Cortical Thickness

- Shape Analyses

template

individual

individual

template

Automated Morphometry

- Atlas-Based Segmentation:

  template

  ↓

  individual

- Voxel-Based Morphometry (VBM):

  individual

- Tensor-Based Morphometry (TBM):

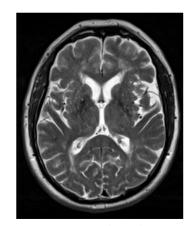 ↓

  template

- Cortical Thickness

- Shape Analyses

Tamburo, Aizenstein, et al., 2007, ISBI
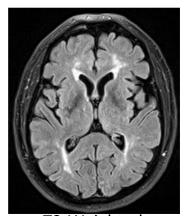
T2-Weighted (with or without FLAIR)

- Weighted towards imaging differences in T2 (transverse) relaxation properties of tissue.

- Long TR, short TE

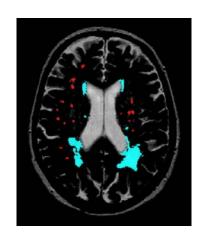- Often used with FLAIR to accentuate WMH/CSF contrast

T1-Weighted

T2-Weighted

T2-Weighted FLAIR

White Matter Hyperintensities (WMH)

- Areas of hyperintensities found on MRI images, best seen in T2-weighted   FLAIR images.

- Located around ventricles (periventricular) and in deep WM.

- Caused by white matter alterations such as demyelination, gliosis, or axonal degeneration

- Most studies point to a vascular (ischemic) origin for WM changes

Clinical Significance

- Some studies have shown an association between WMH and disorders of aging including

  - Cognitive deficits

  - Depression

Vascular Depression Hypothesis of LLD

Cerebral small vessel disease contributes to the occurrence and perpetuation of depression in some older adults. (Alexopoulos, 1989)

Evidence:

- WMHs (subcortical) associated with LLD (Hickie et al, 1997; Krishnan, 1997)

- DTI shows WM changes assoc. with poor response. (Alexopoulos, et al., 2002)

- Decreased resting CBF/metabolism in PFC, caudal ACC, striatum in LLD (Nobler et al., 1999; Meltzer et al. 1998)

- LLD show impairment on executive and speed tasks associated with poor response (Alexopoulos et al., 2000)

Measurement of WMH
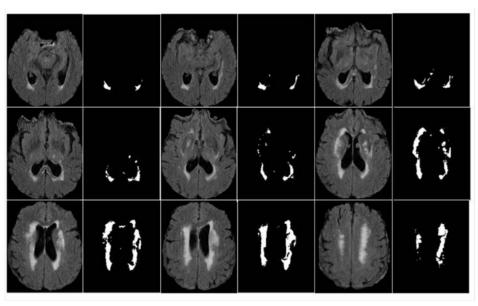
Two approaches used to evaluate WMH on FLAIR images:

Visual rating systems

- WMH severity is visually graded by trained experts
- High variability based on rater and scales
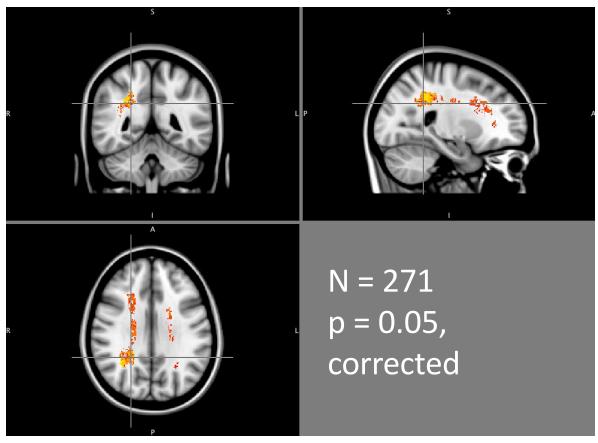
Computer-assisted volumetric evaluation

- More reliable than visual ratings
- Allows for accurate localization and volumetric analysis of WMH

Automated WMH Segmentation

- Fuzzy connected algorithm to segment the WMH
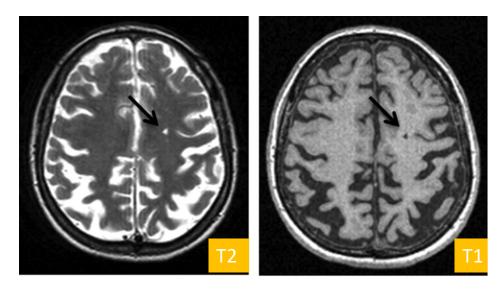- Left-side is unprocessed FLAIR, right-side is segmented WMH

Wu, Aizenstein et al., 2006

Distribution of WMH with Depressive Symptoms

N = 271
p = 0.05, corrected

From Health ABC study, Rosano, Aizenstein, Tudorascu

Strokes (including Lacunes)

Some partially automated methods, generally done manually.

Population Neuroscience

How is MRI research relevant for population studies?

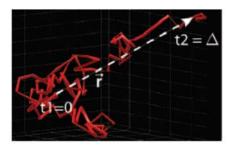Isn't it only for small sample, mechanistic studies?
- Cost isn't prohibitive.
- Number of population based studies with 100's and 1000's of participants. CHS, Health ABC, WHI, BLSA, ADNI

How can it guide public health?
- Examples: New biomarkers for AD diagnosis, concept of pre-clinical AD.
- MRI can serve as proxy-outcome for intervention studies.
- And as a neuroendophenotype for behavioral disorders

Diffusion Weighted Imaging
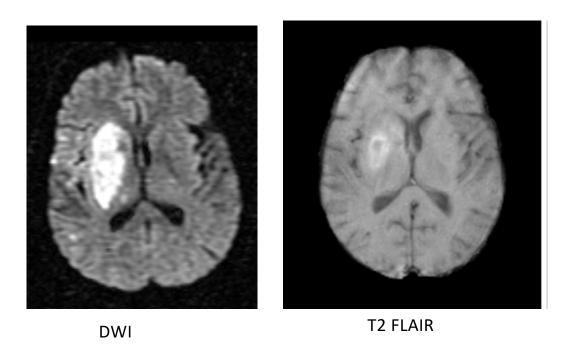
- ## Diffusion or Brownian Motion
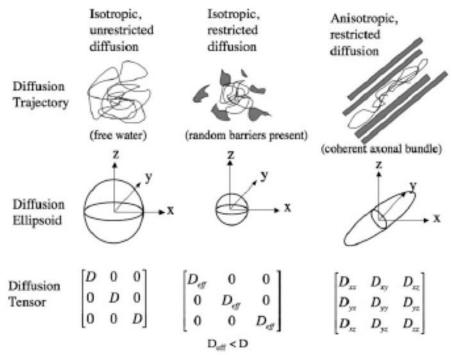

Hagmann, Radiographics, 2006

- Attenuation of the signal due to diffusion is acquired using pulsed excitation gradient in different directions.

- Used clinically as early indicator of stroke (cell swelling)

- Advanced methods such as DTI, DSI, HDFT used to assess myelin integrity and do fiber tracking.

Diffusion Imaging

- Raw diffusion images for detecting stroke

DWI

T2 FLAIR

Diffusion Tensor Imaging
(An)isotropic diffusion

Mukherjee et.al., AJNR (2008) 29, 632-641

Fractional Anisotropy: a measure of directional diffusivity.
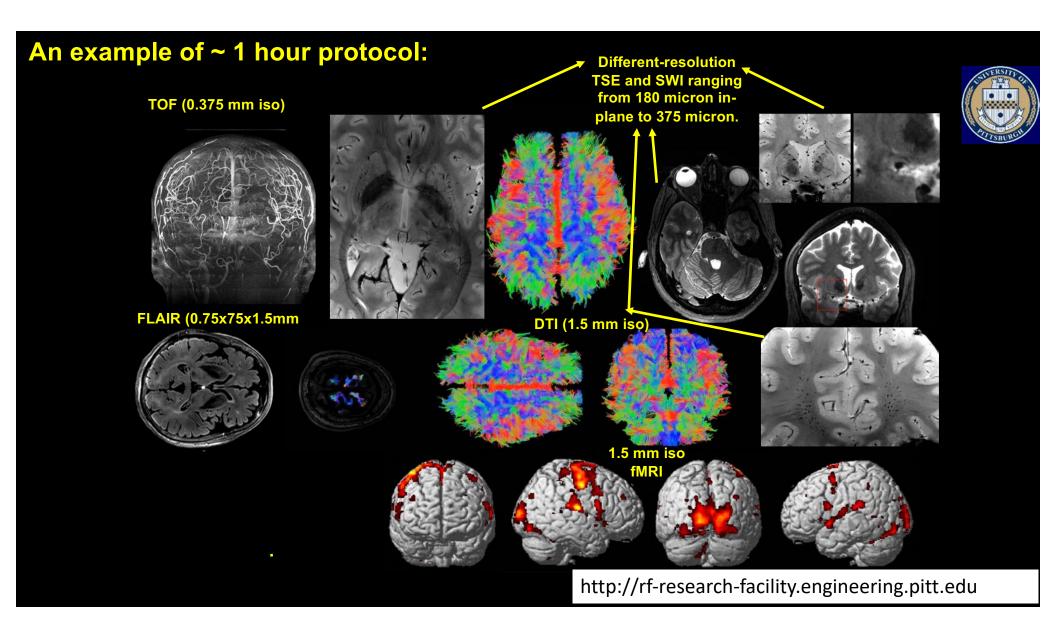Higher   greater myelin integrity.

Highlights of the Translational Studies in the 7 Tesla Bioengineering Research Program

All of the 7 Tesla data were obtained using the Tic Tac Toe RF Coil System (conceived and developed in the RF Research Facility).

Tamer S. Ibrahim (PI)

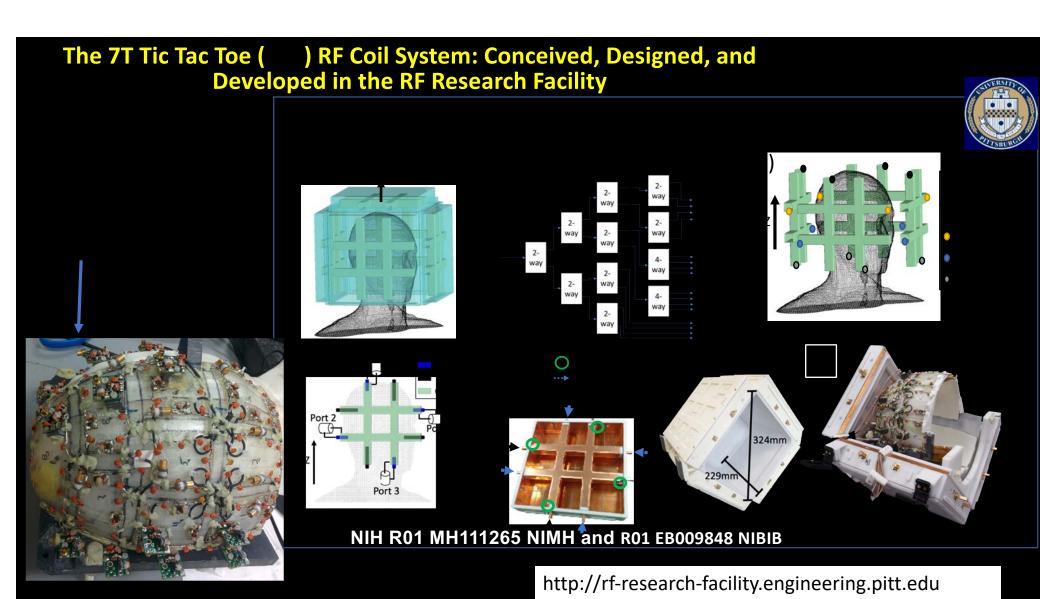http://rf-research-facility.engineering.pitt.edu
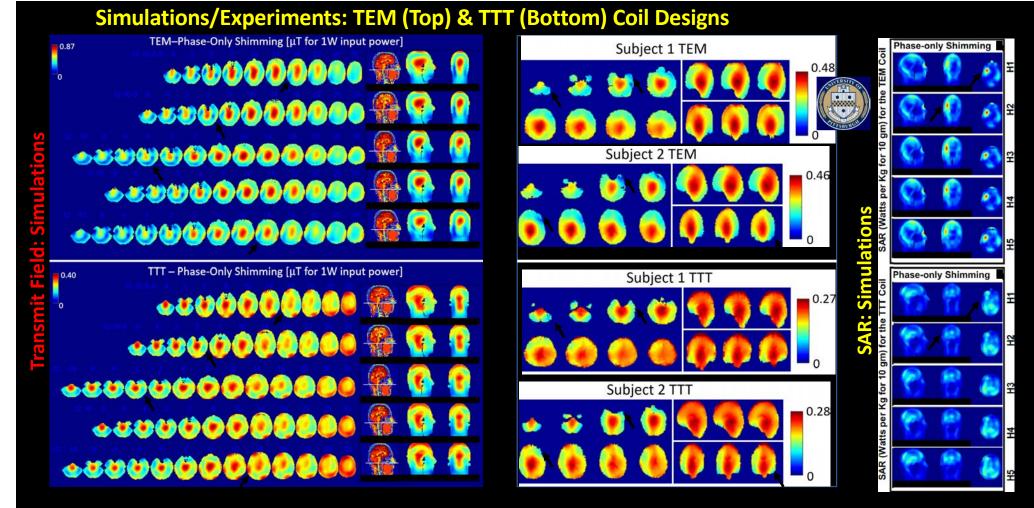
An example of ~ 1 hour protocol:

TOF (0.375 mm iso)

Different-resolution TSE and SWI ranging from 180 micron in-plane to 375 micron.

FLAIR (0.75x75x1.5mm

DTI (1.5 mm iso)

1.5 mm iso fMRI

http://rf-research-facility.engineering.pitt.edu

MRI Modalities:

- T1-Weighted ('Anatomic')
  - Morphometry: regional volumetrics, cortical thickness, shape
  - Perivascular spaces   .

- T2-Weighted (with or without FLAIR)
  - WMH, lacunes
  - Anatomic landmarks

- SWI (Susceptibility weighted Imaging)
  - Microbleeds, perivascular spaces, vessels, anatomic landmarks

- TOF, CSF pulsatility

UHF (7T) MRI

- Increased SNR due to aligning more protons
- Challenge Larmor wavelength through tissue at 7T is 11 cm
- Leads to inhomogeneities.
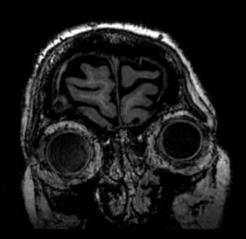- RF solution with Tic-Tac Toe design

http://rf-research-facility.engineering.pitt.edu

The 7T Tic Tac Toe (   ) RF Coil System: Conceived, Designed, and Developed in the RF Research Facility

NIH R01 MH111265 NIMH and R01 EB009848 NIBIB

http://rf-research-facility.engineering.pitt.edu

Simulations/Experiments: TEM (Top) & TTT (Bottom) Coil Designs

Transmit Field: Simulations

TEM–Phase-Only Shimming [µT for 1W input power]

TTT – Phase-Only Shimming [µT for 1W input power]

Subject 1 TEM

Subject 2 TEM

Subject 1 TTT

Subject 2 TTT

SAR: Simulations

Phase-only Shimming

SAR (Watts per Kg for 10 gm) for the TEM Coil

Phase-only Shimming

SAR (Watts per Kg for 10 gm) for the TTT Coil

H1
H2
H3
H4
H5

TTT requires higher RF power

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T1-weighted
MPRAGE

Enhanced GM contrast at 7T

- Well visualized substructure anatomy of the hippocampus at 7T.
- Radiofrequency (RF) field inhomogeneities are mitigated using the 7T Tic Tac Toe RF coil system.
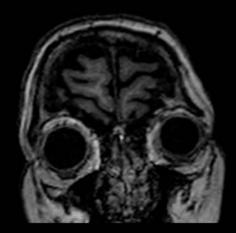- Extended RF field coverage to temporal lobe & cerebellum even W. RF Power-Intensive T2 scan.

RF Research Facility
http://rf-research-facility.engineering.pitt.edu

Small Vessel Disease/Late-Life Depression Study (7T)   Small Vessel Disease/Late-Life Depression Study (3T)

NIH R01 MH111265 NIMH

T2-weighted

2D TSE
0.375mm x 0.375mm x 1.5mm
TA = ~3.5min
TR = 10.06s; TE = 61ms

3D SPACE
0.8mm x 0.8mm x 0.8mm
TA = ~6min
TR = 3.2s; TE = 563ms
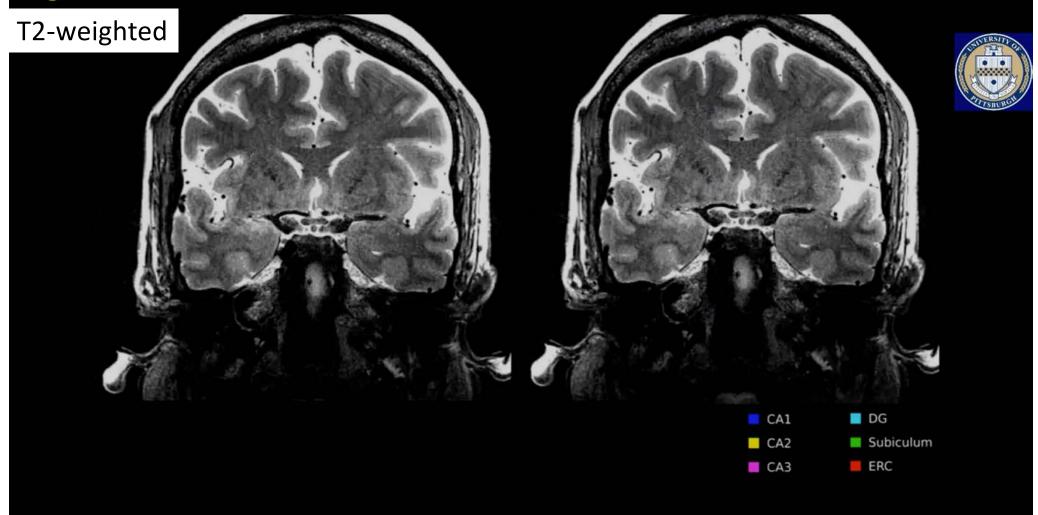
http://rf-research-facility.engineering.pitt.edu

7T Allows for Accurate and Highly Detailed Automatic Hippocampus Segmentation (Midlife Neurocognitive Disparities: NIH R01 DK110041 NIDDK)
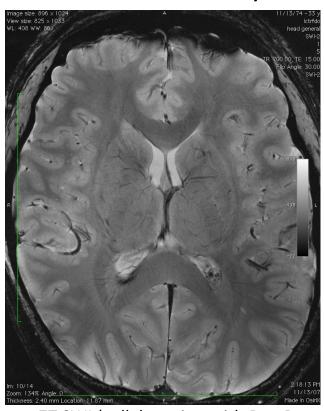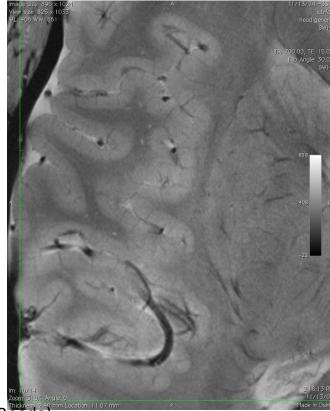
RF Research Facility
http://rf-research-facility.engineering.pitt.edu

T2-weighted

- CA1
- CA2
- CA3
- DG
- Subiculum
- ERC

Susceptibility-Weighted Imaging

- Combination of phase and magnitude, enhances 'susceptibility signal'

- Contrast scales very well with increasing field strength

- Identifies microbleeds: prominent in cerebral amyloid angiopathy and increasingly recognized as important marker of cerebrovascular integrity in elderly.

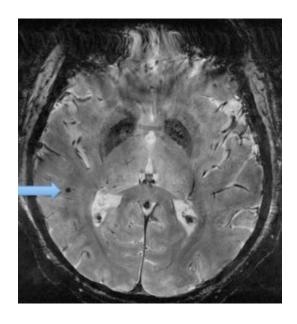- Images venous side of vascular tree.

- Quantitative Iron.

Susceptibility-Weighted Imaging

- Contrast scales very well with increasing field strength

7T SWI (collaboration with Drs. Rosano and Boada)

Susceptibility-Weighted Imaging

- Identifies microbleeds: prominent in cerebral amyloid angiopathy and increasingly recognized as important marker of cerebrovascular integrity in elderly.
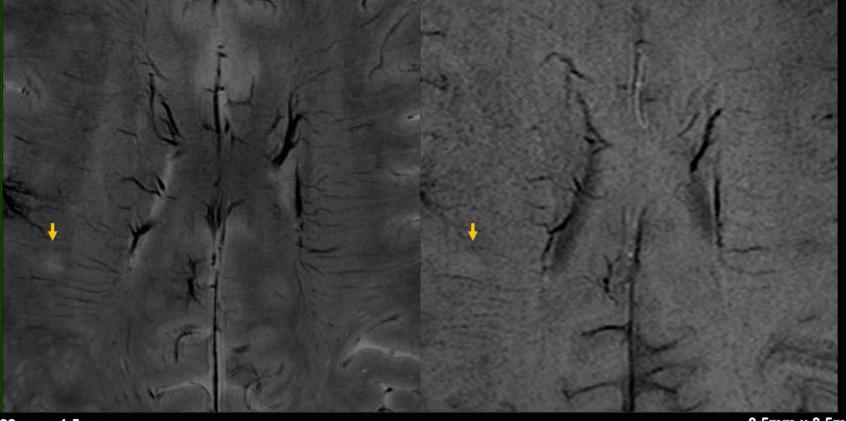

7T SWI

Susceptibility-Weighted Imaging

- Images venous side of vascular tree (deoxygenated hemoglobin)

- Zoomed previous slide: Much better visualization (at 7T) of medullary veins in the deep periventricular white matter (see many more vessels, also the vessels are better defined).
- White matter lesion with a traversing vein (can not be visualized at 3T). White matter lesion without any convincing traversing vein (can not be visualized at 3T). There is value in discerning these two subtypes of white matter lesion to distinguish traditional small vessel disease from an inflammatory component.

Healthy Brain Initiative Study (7T)

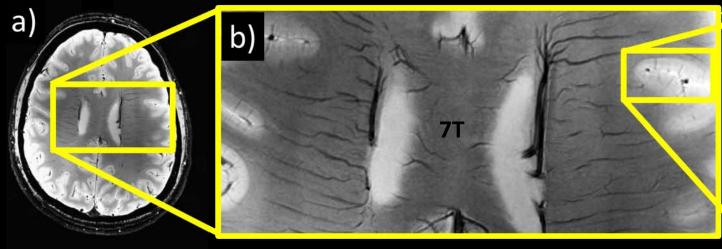**NIH RF1/R01 AG025516 NIA**
Normal Aging Study (3T)

2D SWI
0.22mm x 0.22mm x 1.5mm
TA = ~10min
TR = 1.96s; TE = 14ms

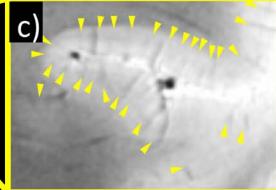3D SWI
0.5mm x 0.5mm x 1.5mm
TA = ~9min
TR = 28ms; TE = 20ms

Susceptibility Weighted Imaging (0.2 x 0.2 x 1.5 mm^3) shows cortical microvessels at sub 100 microns *in-vivo*
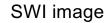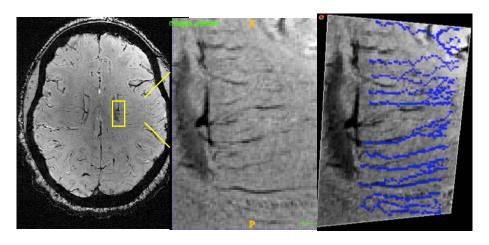

Fig. 2.—Arteriolar supply to cortex. Light photomicrograph of 100-μm celloidin section with alkaline phosphatase vascular stain, counterstained with cresyl violet acetate and light green. Medium-sized pial artery and vein are encased in common connective tissue sheath in space between two gyri. Cortical arterioles penetrate cerebral surface. It is possible to differentiate gray matter from white matter by density of capillary bed. This is an example of single supply with adjacent arterioles arising from a common source. Cortical arterioles share capillary network. Note capillary-free zone (arrows) surrounding alkaline phosphatase-stained arterioles, which is anatomic evidence that arterioles have a primary nutritive responsibility to their surrounding neural tissues. This was observed [4] prior to general recognition of this fact by physiologists [5]. This periarteriolar capillary-free zone will not be easily distinguished on thicker specimens imaged with microradiography because of superimposed capillaries above and below particular arteriole. (See Fig. 4.) Bar = 500 μm.

BrainVein

- Computer Vision algorithm for Segmentation of medullary small veins from UHF SWI.
- Takes advantage of known radial orientation of vessels

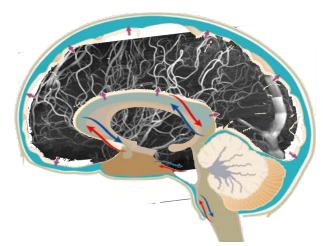SWI image   Segmented 3D veins
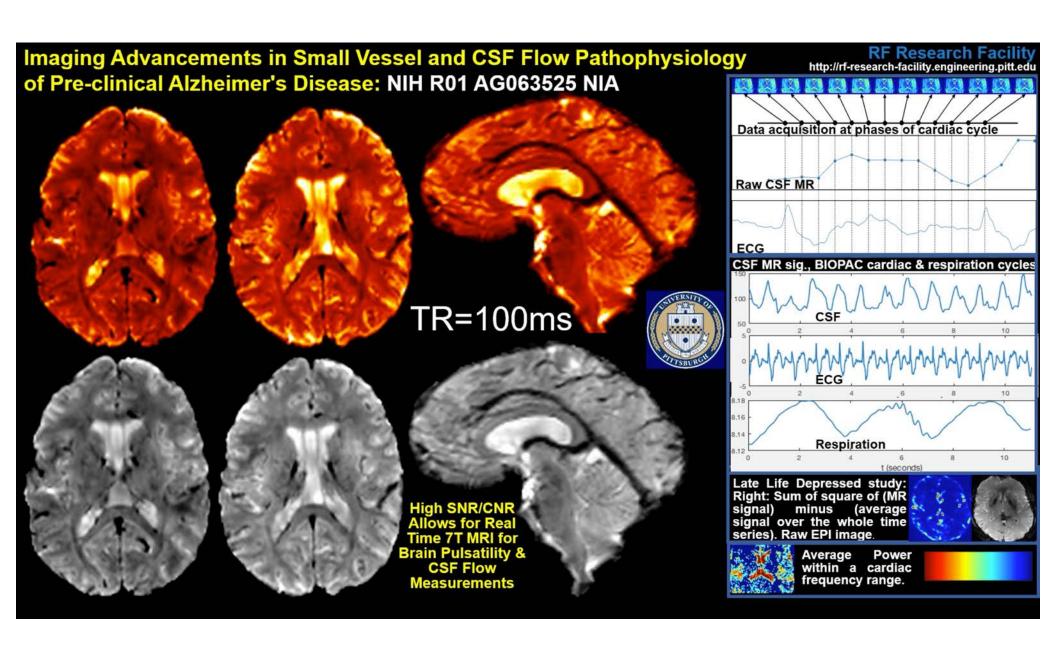
Stetten et al., CARS 2019

G. Stetten, Minjie Wu.

Role of CSF Clearance in late-onset AD

- Amyloid and other neurotoxic metabolites are cleared through CSF
- Decreased clearance is salient model for late-onset AD
- The CSF is formed from interstitial fluid pushed along small channels from pulsations in the vessels
- Related to delta-waves (slow-wave sleep).
- Team of investigators addressing this including bioengineers and sleep researchers.

BIOE RF Lab: Tamer Ibrahim. Tales Santini, Tiago Martins

Kristine Wilckens, Minjie Wu, Caterina Rosano, Joe Mettenburg

Imaging Advancements in Small Vessel and CSF Flow Pathophysiology of Pre-clinical Alzheimer's Disease: NIH R01 AG063525 NIA

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TR=100ms

High SNR/CNR Allows for Real Time 7T MRI for Brain Pulsatility & CSF Flow Measurements

Data acquisition at phases of cardiac cycle

Raw CSF MR

ECG

CSF MR sig., BIOPAC cardiac & respiration cycles

CSF

ECG

Respiration

t (seconds)

Late Life Depressed study: Right: Sum of square of (MR signal) minus (average signal over the whole time series). Raw EPI image.

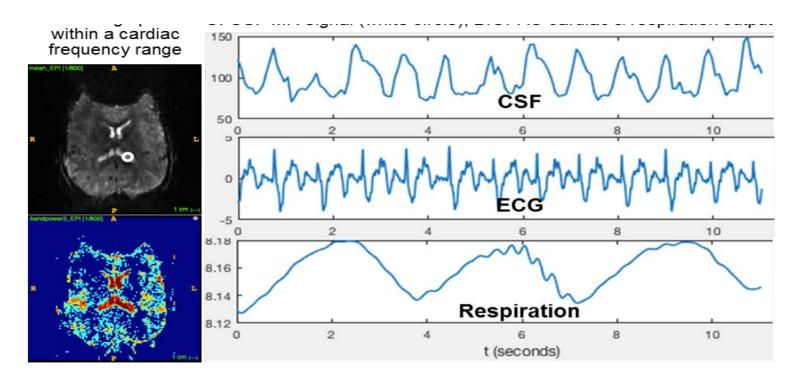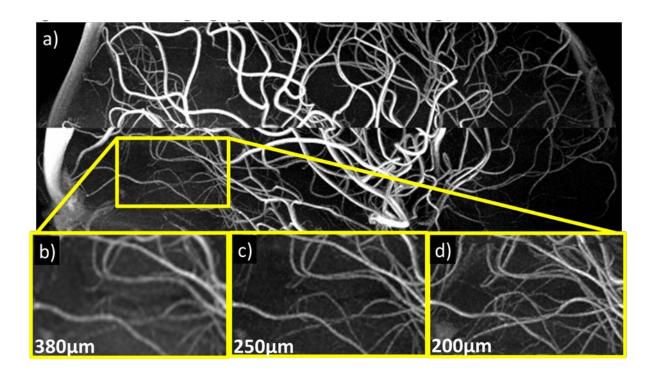Average Power within a cardiac frequency range.

100ms TR: Bold Contrast

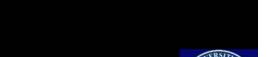**BIOE RF Lab:** Tamer Ibrahim. Tales Santini, Tiago Martins

And Pulsatility

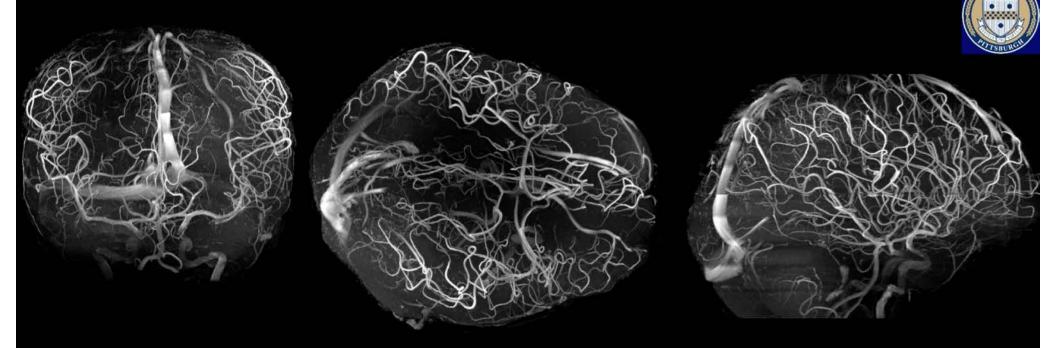**BIOE RF Lab:** Tamer Ibrahim. Tales Santini, Tiago Martins

High resolution MR angiography without contrast

BIOE RF Lab: Tamer Ibrahim. Tales Santini, Tiago Martins

7T Time of Flight Imaging Allows for Unprecedented Resolutions without Contrast Agents *in-vivo* (Schizophrenia Study: NIH R21 MH101566 NIMH)

RF Research Facility
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$(0.375 \times 0.375 \times 0.375 \text{ mm}^3)$
Whole Head (15-cm), Total scan time ~ 12min

Future Directions

A current research challenge involves relating the different image modalities, essential for translational research.

Mechanism:

Can UHF imaging identify the cellular or microstuctural features that explain altered function?

Biomarkers:

Statistical approaches, including machine learning, combine across different modalities to better identify predictors of treatment response. (personalized medicine)