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HST.583 Functional Magnetic Resonance Imaging: Data Acquisition and Analysis
Fall 2008

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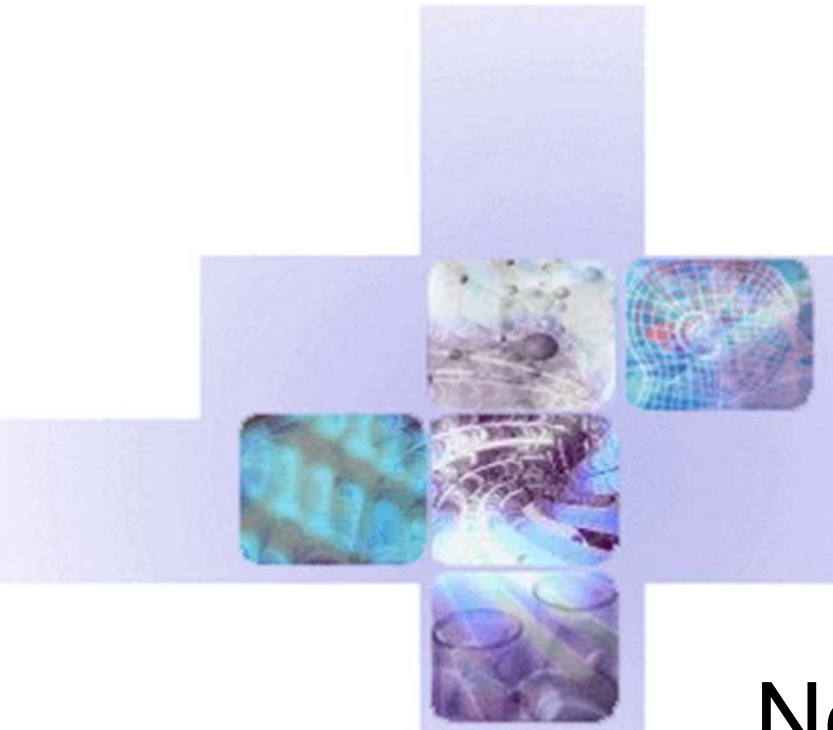

BIRN

Quantitative Neuroimaging Biomarkers

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National Center for Research Resources

National Institutes of Health

Dec. 3, 2008, HST 583

Overview

- Biomarkers
  - must have a scientific basis
  - a change in the marker must reflect a change in disease progression
  - be measurable and reproducible

Non-cognitive biomarkers are often used because cognitive measures often do not have a tight link to disease severity modifications.

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Overview

- The goal of biomedical imaging is to understand biophysical processes. Visualization can aid understanding.
- As medical knowledge progresses, the effects we study become ever more subtle.
- Statistically, we then need a larger number of independent measurements to get accurate and precise results for subtle effects. → acquire data at multiple sites…

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Overviews

- Which biomarkers are predictive?

  - do they track with disease progression and treatment effect?

- Can we measure these biomarkers in a multi-site trial, i.e., what is the size of the variability of:

  - site effects?

  - subject effects?

  - choice of processing algorithms and input parameters?

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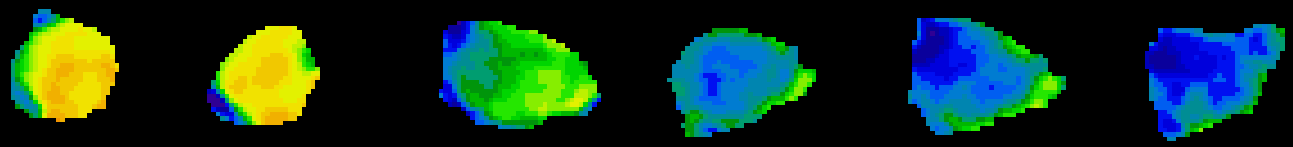
Overview – Example I

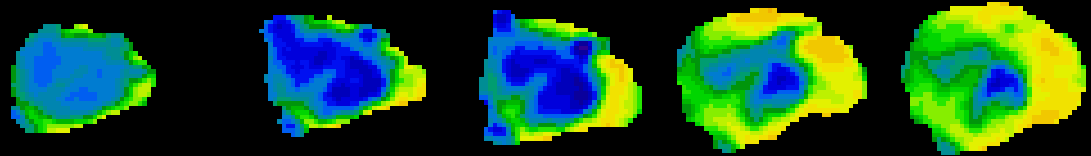
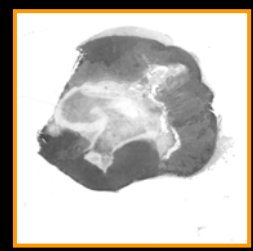
- Non-neuroimaging example:

With imaging, we can visualize the effect of the drug, which can help decide drug efficacy. Later, it can monitor the effects of refinement in the drug formulation and dosing.

Overview – Example I

Treatment, 100mg/kg 5-FU

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
ADC						
Tumor Volume	0.60 cm^3	0.70 cm^3	0.95 cm^3	0.86 cm^3	0.71 cm^3	0.76 cm^3

	Day 7	Day 8	Day 9	Day 10	Day 11	Histology
ADC						
Tumor Volume	1.13 cm^3	1.36 cm^3	1.60 cm^3	1.79 cm^3	2.08 cm^3	

Overview – Example II

What if the disease effect on the biomarker is small?

"Several studies by Jack et al. (1998, 2000, 2004) of older sporadic AD cases (mean ages 74–79 years in the different studies) have reported annualized rates of hippocampal atrophy of 3–4% with age-matched controls (mean ages 77–80 years) having rates of atrophy of 1.4–1.7% per year and similarly aged MCI subjects have intermediate rates at 1.8–3.7% per year."

- from "Differentiating AD from aging using semiautomated measurement of hippocampal atrophy rates." Barnes J, Scahill RI, Boyes RG, Frost C, Lewis EB, Rossor CL, Rossor MN, Fox NC. Neuroimage. 2004:574-81.

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Alzheimer's Disease

- Clinical symptoms of AD are due to the loss of neurons and loss of viable connections between neurons.
- The medial temporal lobe (MTL) has the highest density of histopathological markers.

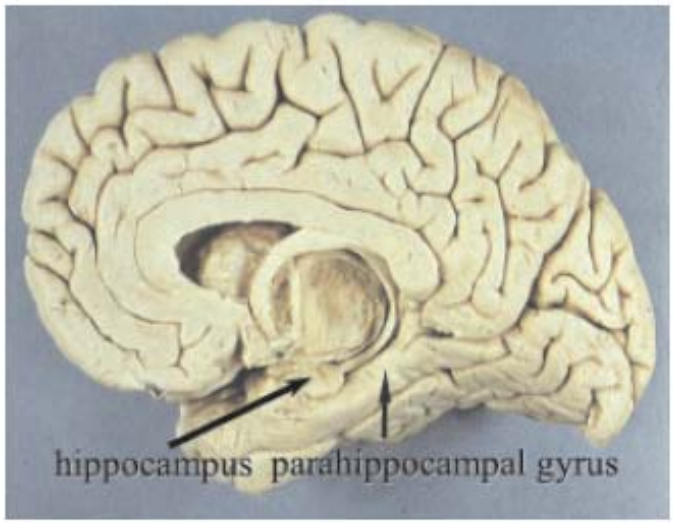

Fig. 1. Photograph of the median aspect of the human brain (front to left) showing two parts of the MTL, the hippocampus, and parahippocampal gyrus. The third part is the amygdala.

Deficits in verbal memory correlate with atrophy in left hippocampal volume and deficits in non-verbal memory correlate with atrophy in the right hippocampal volume.

From "Imaging the progression of Alzheimer pathology through the brain." David A. Smith, *Proc Natl Acad Sci* U S A. 99 (April 2,2002): 4135–4137.

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Alzheimer's Disease

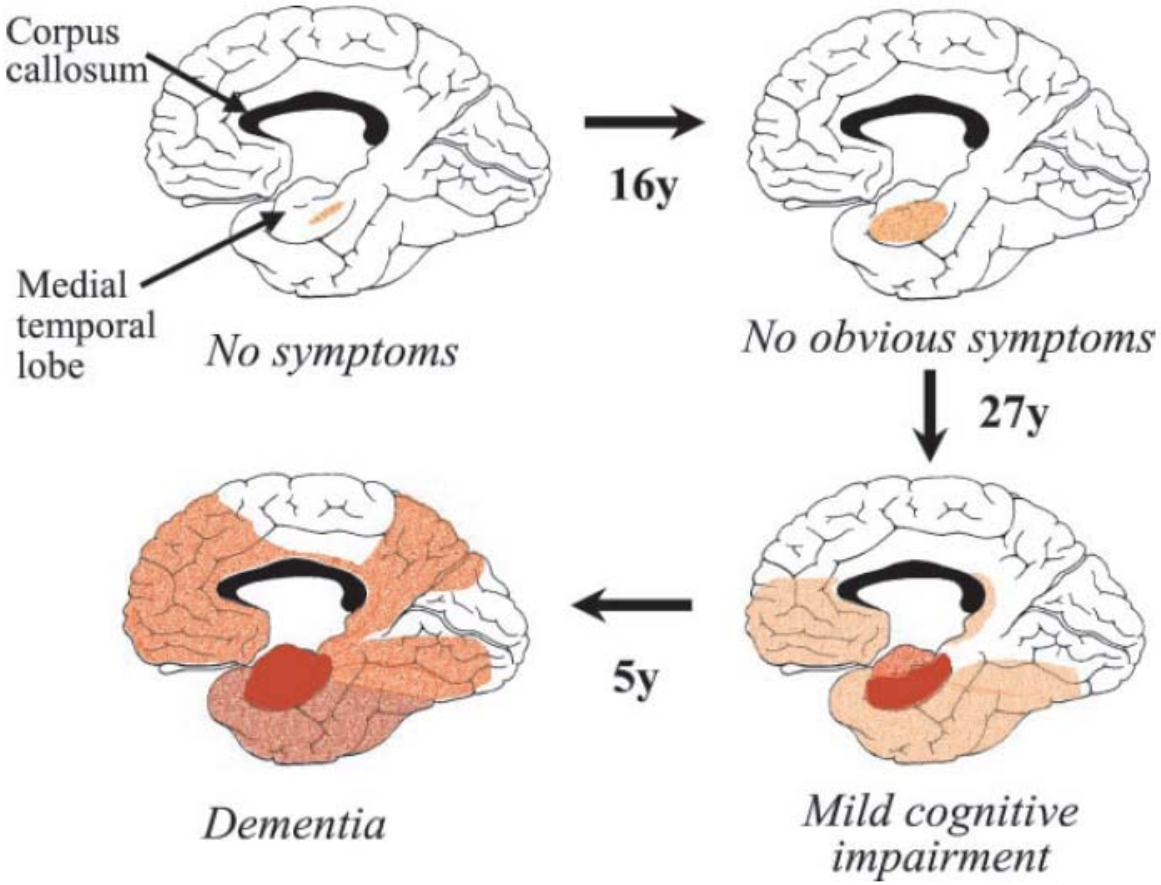

Fig. 3. Postulated sequence of spread of neurofibrillary pathology in AD, showing the medial aspect of the cerebral cortex. The depth of the red color is in proportion to the density of tangles (based on refs. 24 and 28). Several of the red areas showed atrophy in the study by Scahill *et al.* (6).

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From "Imaging the progression of Alzheimer pathology through the brain." David A. Smith, *Proc Natl Acad Sci* U S A. 99 (April 2, 2002):4135–4137.

ADNI – Biomarkers for AD

- Alzheimer's Disease Neuroimaging Initiative

A longitudinal multisite study of elderly people with either mild cognitive impairment (MCI, N=400), Alzheimer's Disease (AD, N=200) or normal cognition (N=200).

Data was collected at 55 sites.

Half of the subjects were imaged using FDG positron emission tomography (PET). All were imaged using MRI on a 1.5T scanner with a structural imaging protocol.

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ADNI

- Healthy controls sampled at: 0, 6, 12, 24, and 36 months
- MCI subjects sampled at: 0, 6, 12, 18, 24, and 36 months
- AD subjects sampled at: 0, 6, 12, and 24

In addition, urine, serum, and CSF biomarkers were acquired in addition to neuropsychiatric evaluations.

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ADNI

- ADNI Goals:

1)Identify best biomarkers for early diagnosis

2)Identify best biomarkers for following disease progression

3)Develop surrogate endpoints for clinical trials

4)Establish methods for dealing with multisite data

-from “The role of biomarkers in clinical trials for Alzheimer's Disease”. Thal LJ et al. Alz Dis Assoc Disord 20:6-15 (2006).

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ADNI

- ADNI Imaging Goals:

1)Link all data at each time point and share data with public

2)Develop technical standards for imaging in longitudinal studies

3)Optimize acquisition and analysis

4)Validate imaging and biomarker data with psychometric and clinical assessments

5)Improve clinical trial methods

-from The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI Methods. Jack CR et al. JMRI 27:685-691 (2008).

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ADNI – Technical Issues

- While humans can make sense of images with minor artifacts, this is not usually true of automated processing pipelines.

Therefore:

1. use larger fields-of view and many slices
2. no parallel imaging
3. no partial k-space imaging
4. correct for chemical shift artifacts
5. correct for intensity inhomogeneity

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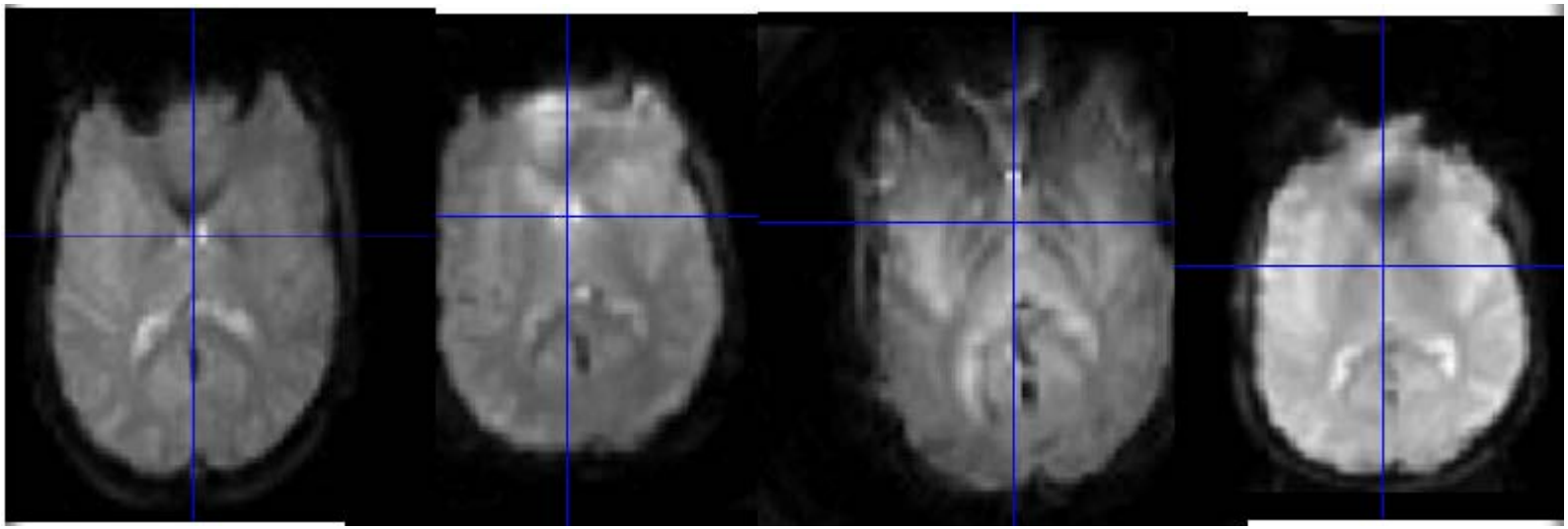
Multi-site Trials

- Variance due to differences in sites!



Same subject, same slice,
different sites ‘best’ scan

Courtesy of Jessica Turner. Used with permission.

Source: Jessica Turner (FBIRN), Univ. California, Irvine

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ADNI – Technical Issues (Optimization)

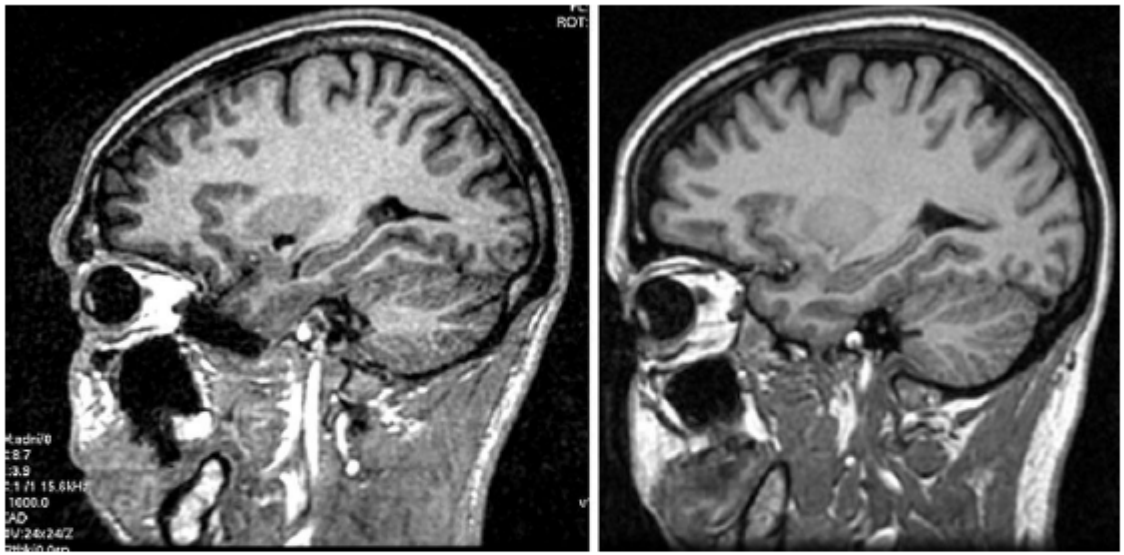

Figure 2.
Poor SNR with single-channel birdcage coils in first version of protocol. As indicated in Table 1, the protocol using a single-channel birdcage coil differs from the phased array protocol. Left: When 1.5 T images are acquired using the phased array protocol with a birdcage coil, poor SNR results. Right: Making the parameter adjustments listed in Table 1 resolves the problem without increasing chemical shift.

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From Jack CR, et al. “The Alzheimer’s Disease Neuroimaging Initiative (ADNI): MRI Methods.” JMRI 27, no 4 (2008): 685-691.

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ADNI – Technical Issues (Artifacts)

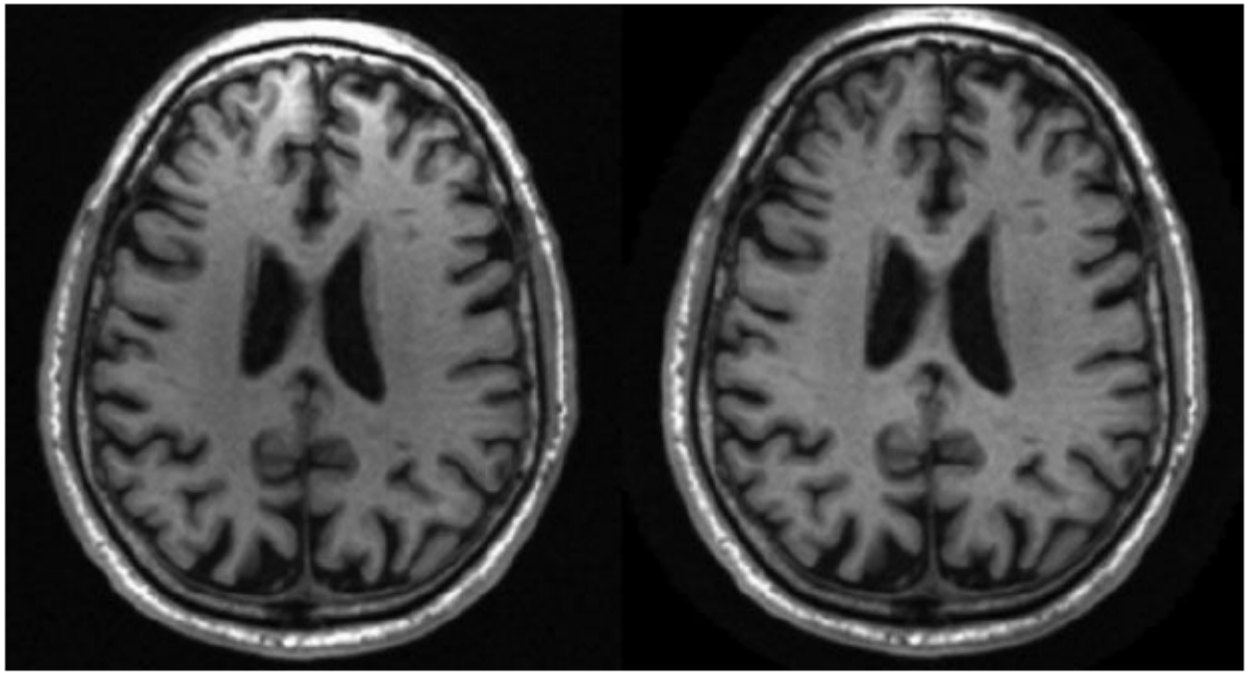

Figure 6.
Intensity in-homogeneity correction. Phased array coil acquisition at 1.5 T before (left) and after (right) intensity nonuniformity correction. Images have been reformatted from the sagittal into the axial plane to illustrate the intensity in-homogeneity anteriority prior to correction.

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From "The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI Methods, Jack CR, JMRI 27:685-691 (2008).

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ADNI – Technical Issues (Artifacts)

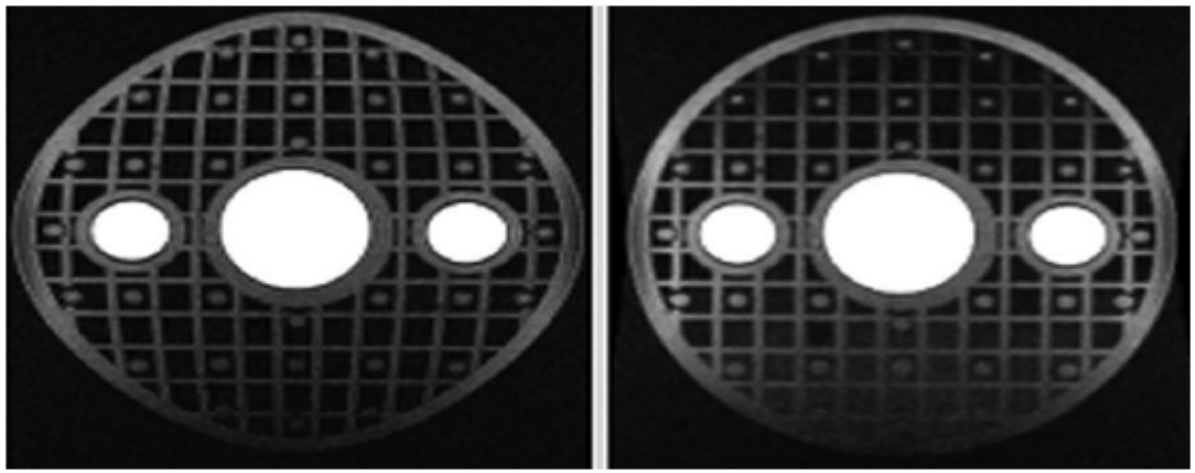

Figure 5.
Effect of gradwarp. Spherical phantom with rectilinear grid inclusion before (left) and after (right) gradwarp correction.

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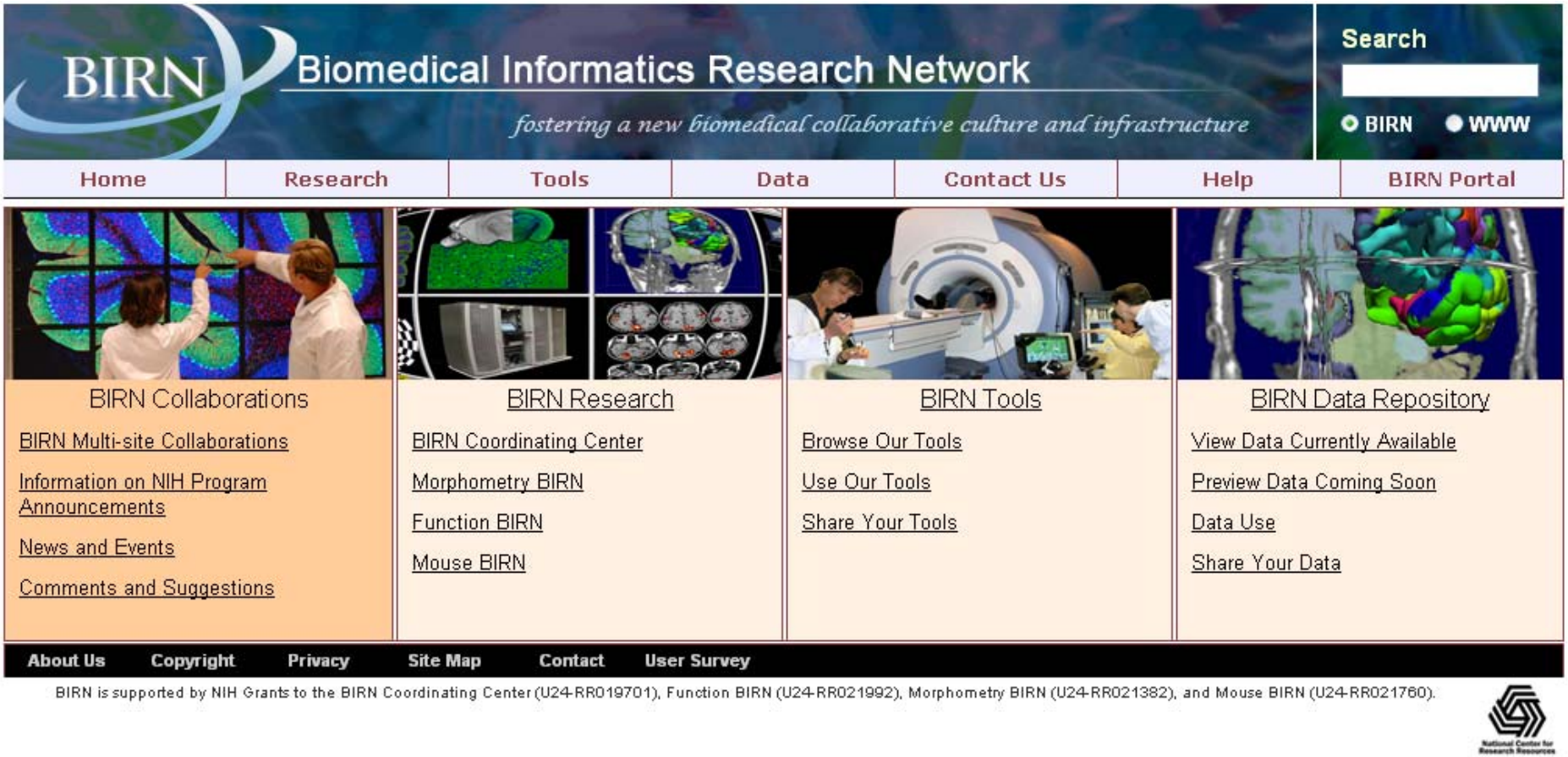
Biomedical Informatics Research Network



www.nbirn.net

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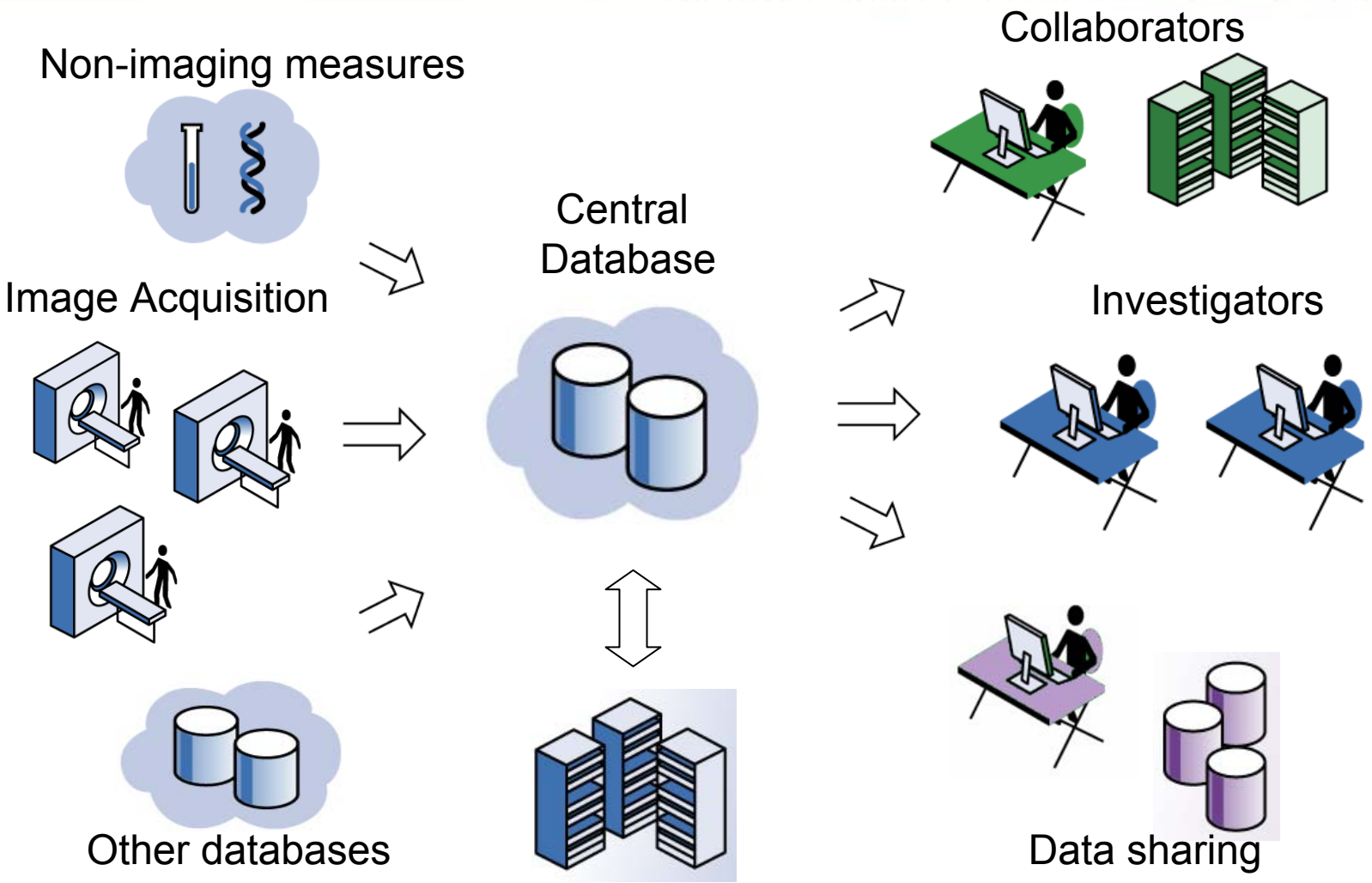
Multi-Center Imaging Study



Source: Dan Marcus (WUSTL)

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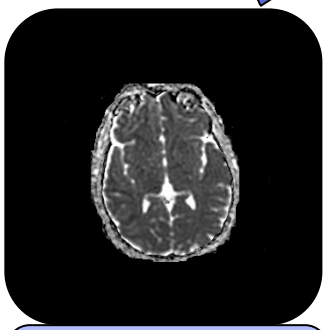
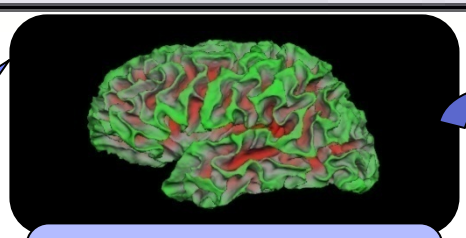
- Overall goal of the Morphometry BIRN:

To develop the ability to process and analyze, as a single data set, MRI data acquired across multiple sites, using tools developed at multiple sites. In addition, to allow data to be shared with the larger community.

mBIRN Data Flow Diagram



Data Acquisition



Data Processing

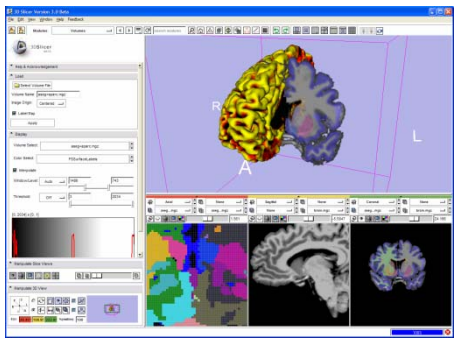
Workflows

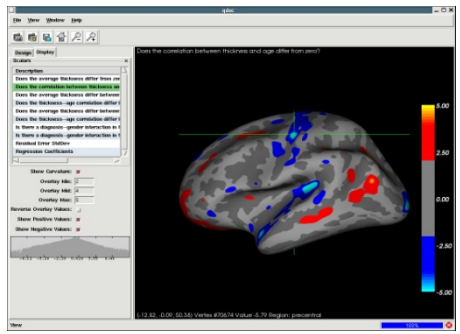
Pipeline | Workbench

Integrate

Database Management

Local XNAT | Remote XNAT | Data Grid





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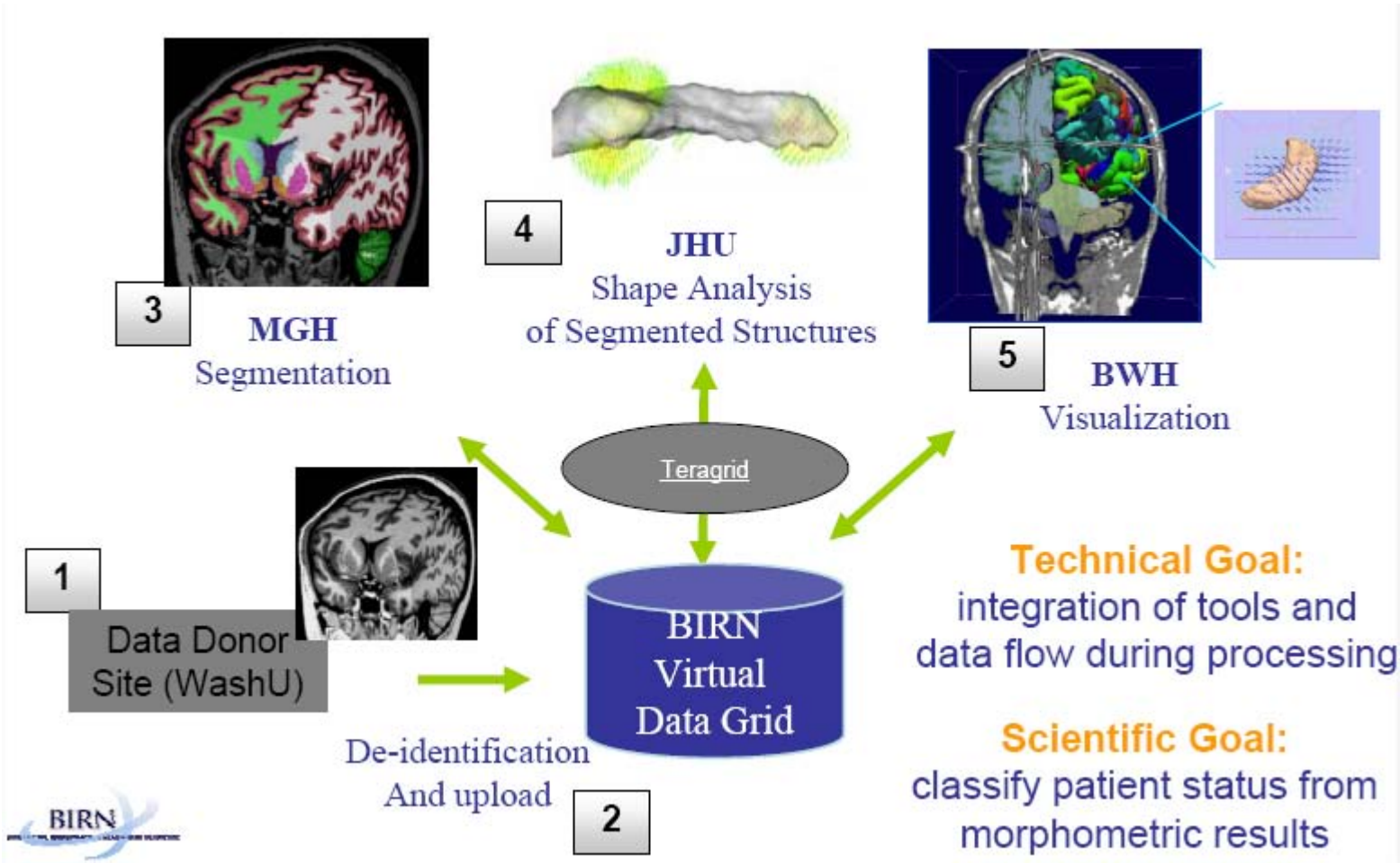
mBIRN Use Case – Shape Analysis in AD



(45 subjects: 21 non-demented controls,
18 very mild Alzheimer's Disease and 6 semantic dementia).

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mBIRN Use Case – Shape Analysis

LD = Linear Discriminant

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(45 subjects: 21 non-demented controls,
18 very mild Alzheimer's Disease and 6 semantic dementia).

mBIRN Use Case – Shape Analysis

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mBIRN Use Case – Shape Analysis

- **2006.05.02** (A. Kolasny)

The 101 subject lddmm processing has been completed. This required 244,824 cpu/hrs of processing and 40TB of storage.

SDSC and NCSA TeraGrid sites, BIRN SDSC cluster and JHU CIS cluster were used for processing the 40,804 lddmm jobs. We will now begin the statistical analysis and visualization processing.

- **2006.03.14** (A. Kolasny)

Added an additional 10TB of storage to the JHU CIS storage repository. This used to complete the right hippocampus processing. Experimenting with sshfs and unionfs to assist in cluster processing.

- **2006.02.10** (A. Kolasny)

Completed lddmm processing for the 101 left hippocampus data sets. This computation required a total of 13 cpu/years of computing. We utilized the JHU CIS cluster, SDSC BIRN Cluster and TeraGrid for the processing. The processing required 20TB of storage which is being stored on the BIRN rack and the TeraGrid /gpfs-wan storage repository. Started processing the right hippocampus data.

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mBIRN Use Case II – Cortical Thickness

- Changes in cortical thickness accompany normal aging, AD, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, …

Can cortical thickness be used as a reliable biomarker?

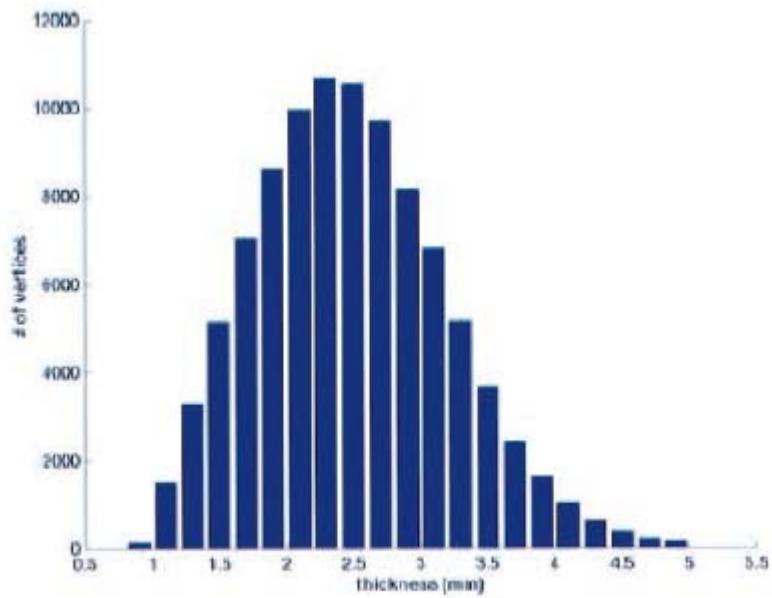

Fig. 3. Histogram of thickness values in cortical regions of the subject shown in Fig. 2. More than 99% of the surface is between 1- and 4.5-mm thick.

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From Fischl, B. and A. M. Dale. "Measuring the thickness of the human cerebral cortex from magnetic resonance images." PNAS 97 (2000): 11050–11055.

mBIRN Use Case II – Cortical Thickness

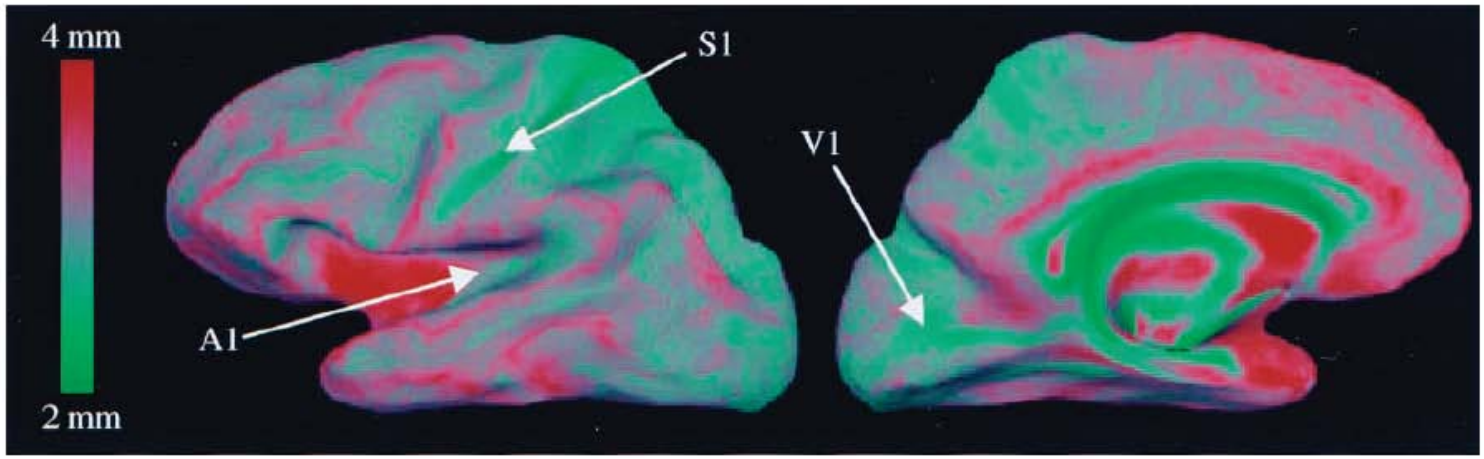

Fig. 4. Average cortical thickness across 30 subjects, with primary auditory (A1), somatosensory (S1), and visual (V1) cortices indicated by the white arrows.

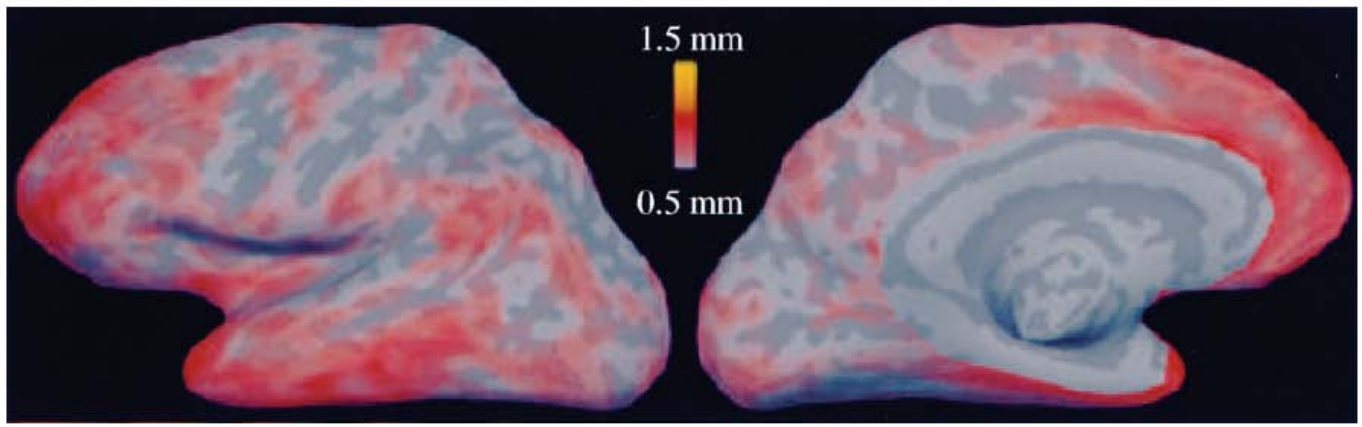

Fig. 5. Map of the standard deviations of the thickness measurements across 30 subjects. Noncortical regions have been excluded on the medial aspect of the surface.

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From Fischl, B. and A. M. Dale. “Measuring the thickness of the human cerebral cortex from magnetic resonance images.” PNAS 97 (2000): 11050–11055.

mBIRN Use Case II – Cortical Thickness

- BIRN cortical thickness reliability study

  -15 healthy older subjects scanned a total of four times. The time between scans was two weeks and three different scanners were used:

Scan 1: Siemens Sonata 1.5T

Scan 2: Siemens Sonata 1.5T (rescan)

Scan 3: GE Signa 1.5T (cross platform)

Scan 4: Siemens Trio 3.0T (cross field strength)

(plus pulse sequence, multiple scans, smoothing)

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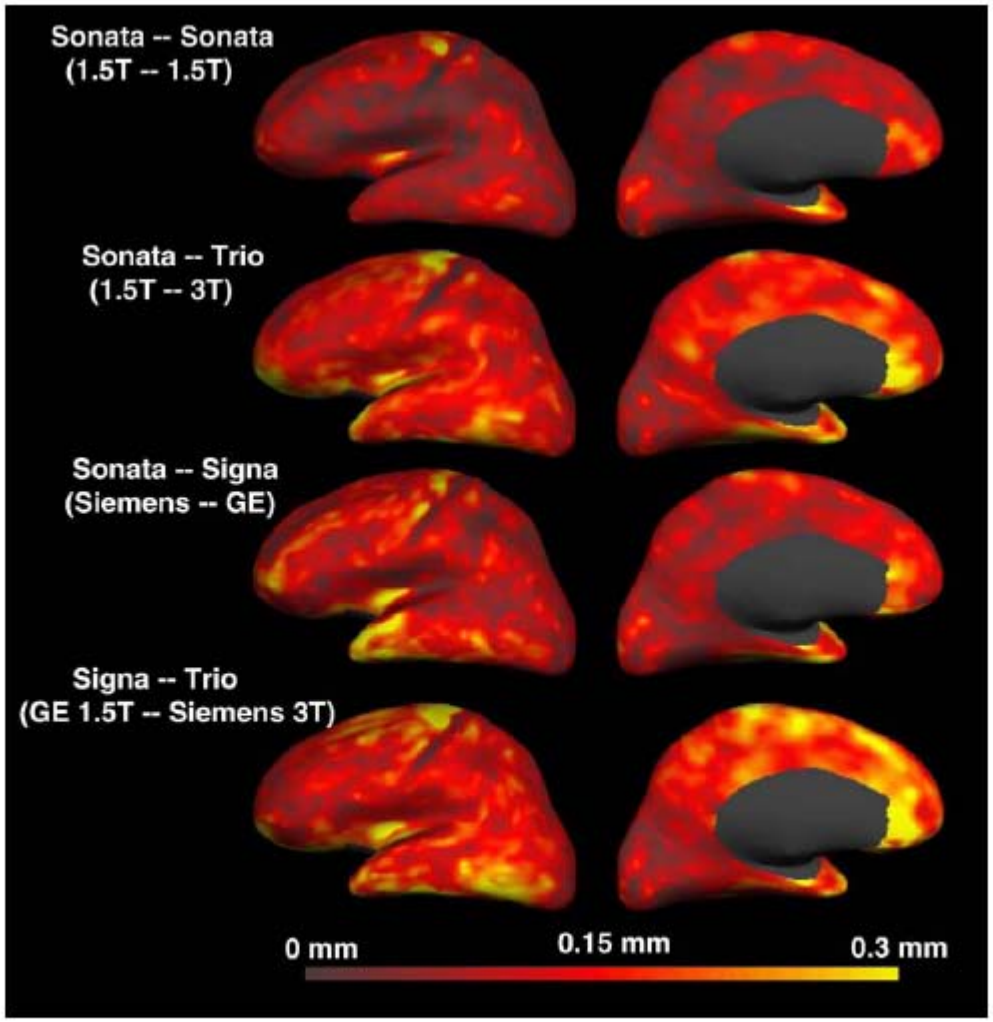
mBIRN Use Case II – Results



From Han, X. et al. "Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade, and munufacturer." *NeuroImage* 32 (2006):180-194.

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Fig. 2. Maps of thickness measurement variability for four test–retest comparisons (the left hemisphere only; the right hemisphere is similar). Subcortical regions and corpus callosum area are masked out since thickness is not defined there. The measurement variability is less than 0.12 mm for most the cortex for the within-scanner test–retest comparison and less than 0.2 mm for across platform comparisons. Left column: lateral view; right column: medial view.

mBIRN Use Case II – Results

- Within-scanner variability < 0.03 mm
- Cross-scanner variability = 0.15 mm
- Cross-field strength variability = 0.17 mm
- Measurements across field strength biased to the higher field strength (thicker)
- No effect from using the average of multiple runs, however using the 1st run as an initial guess for the processing resulted in a statistically significant reduction in variability.

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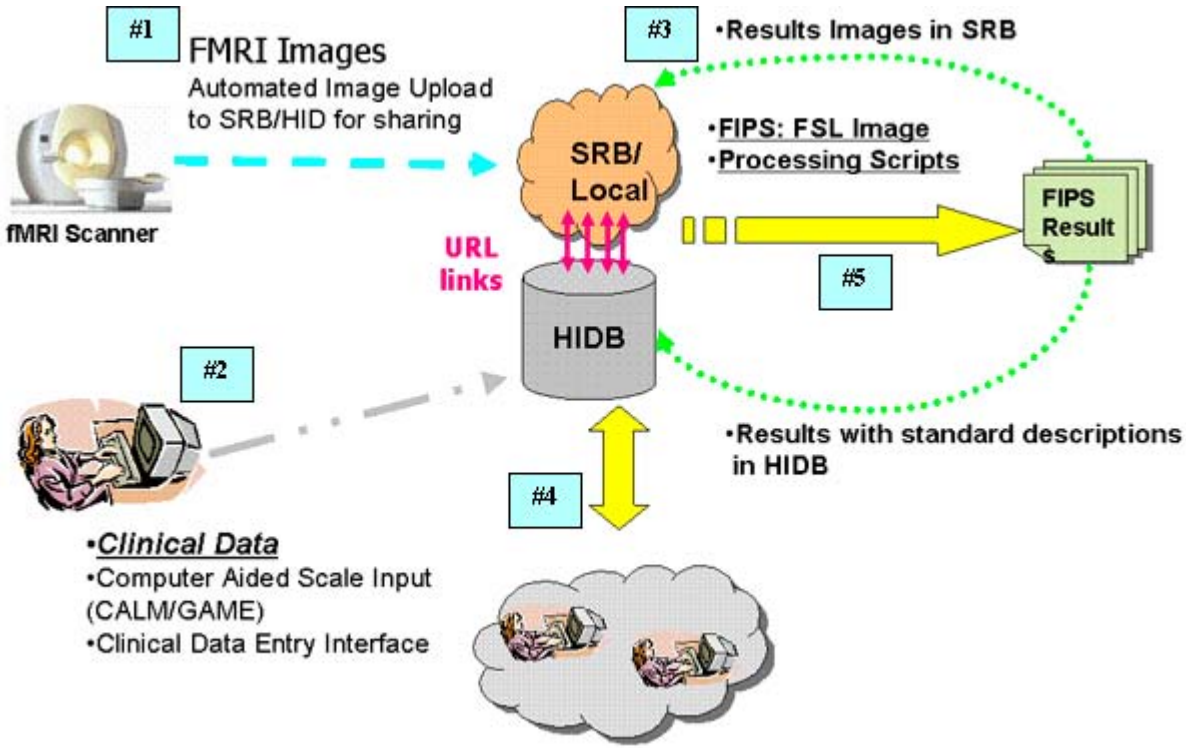
Function BIRN – Multi-site functional MRI

- The goal of the function BIRN is similar to that of mBIRN, but with a focus on functional MR imaging and schizophrenia used as the target population.



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Functional MRI – Multisite Issues

- Differences in:
  - site hardware and software
  - data processing
  - subject's cortical structures
  - subject's activation magnitude on that day
  - brain networks elicited for each task

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Phase I – Travelling Human Phantoms

Courtesy of Jessica Turner. Used with permission.

Subjects traveled around the country to be scanned at all FBIRN sites

Unique dataset: Subject x site interactions can be measured for the first time

Variance Components Analysis

ROI – Top 10% of Activated Voxels			
Variance Source	Auditory	Hand	Visual
Subject	18.8	18.3	21.8
Site	43.0	21.0	43.8
Day	0.0	0.0	0.1
Run	0.4	0.1	0.1
Subject X Site	3.6	14.6	10.5
Subject X Site+	20.7	35.2	20.0
Residual	1.5	4.2	1.5

VCA is a method to identify the individual contributions to the overall variance from the various possible sources.

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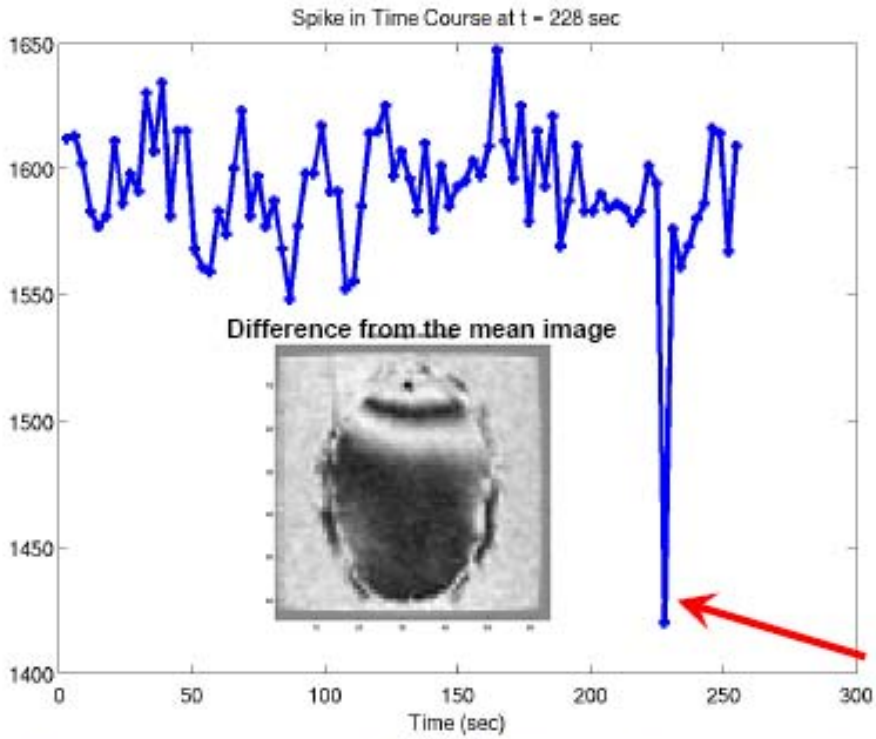
fBIRN Calibration Methods

- **To remove "spikes" that occur in image collection**



- In the traveling subjects dataset, these occurred in .01% of the images
- Looking for them visually is not feasible

- **Automated spike detection and removal allows millions of images to be processed correctly**

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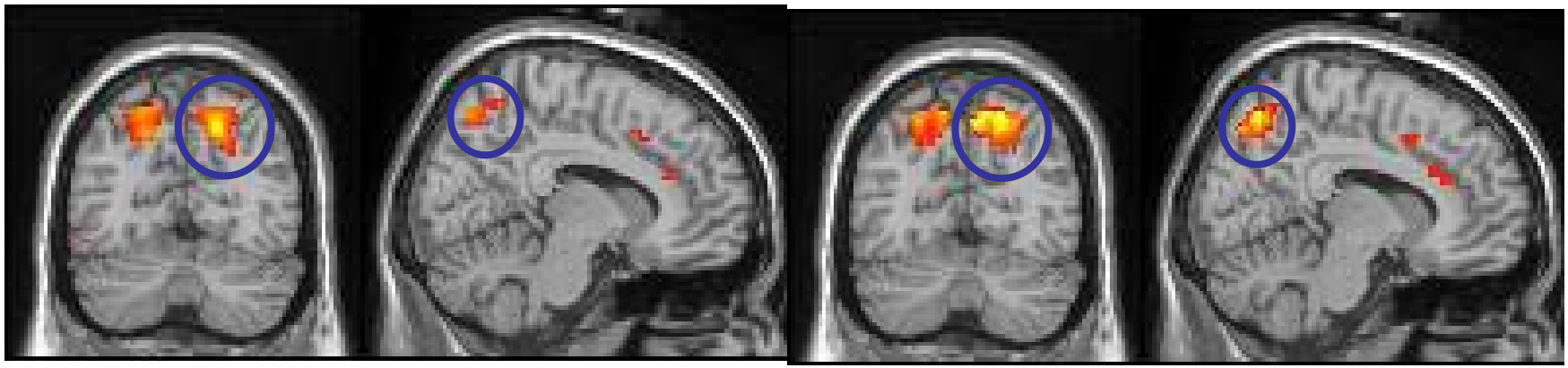
fBIRN Calibration Methods

- Scaling by the breathhold response increases group effect size

Group Differences: **Uncorrected** **Corrected**



Differences between young and old subjects in an fMRI task, before and after correcting for BOLD differences in a separate breathhold task

Courtesy of Jessica Turner. Used with permission.

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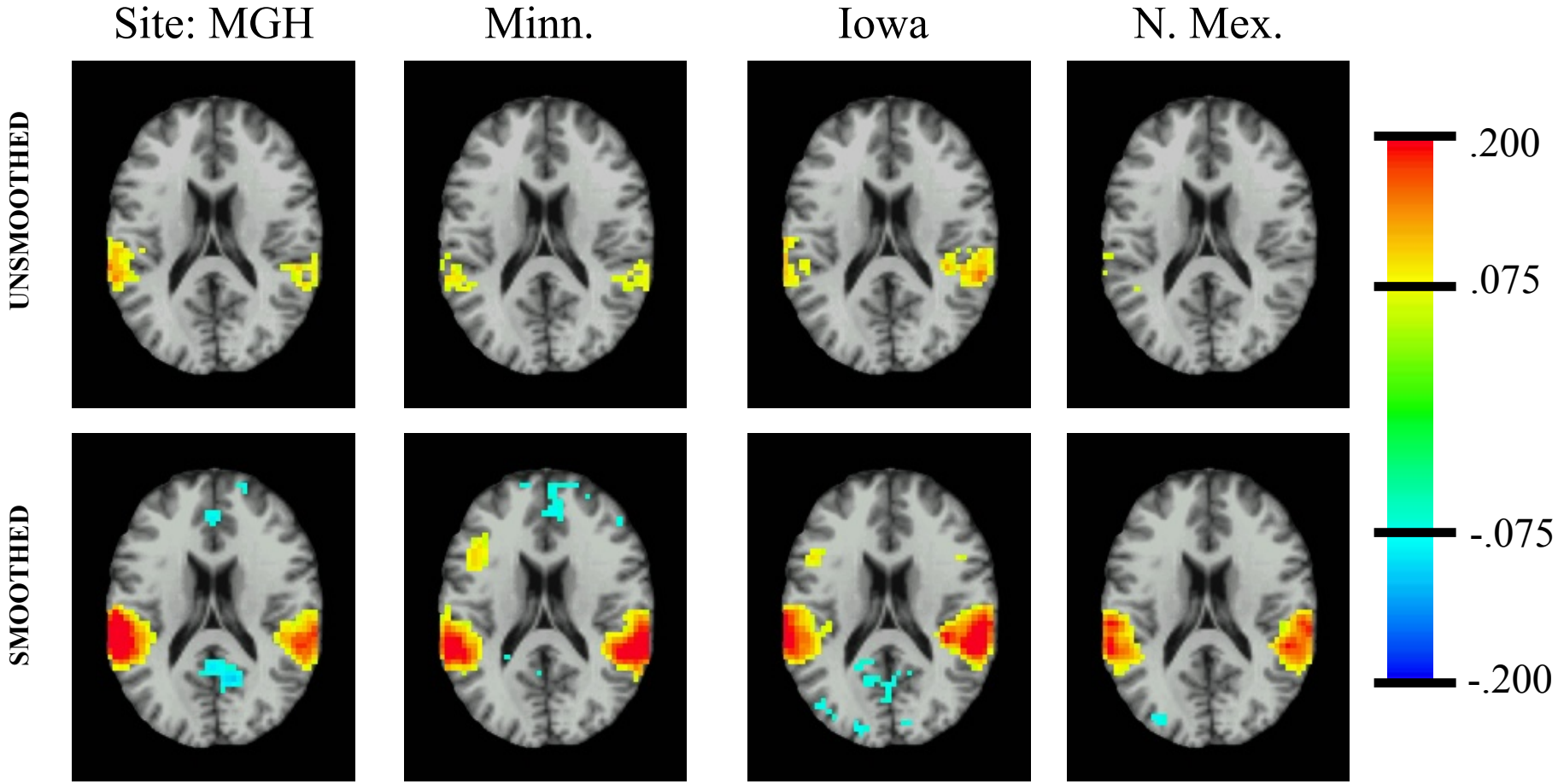
fBIRN Calibration Methods

Smoothing to a common level reduces inter-site effects



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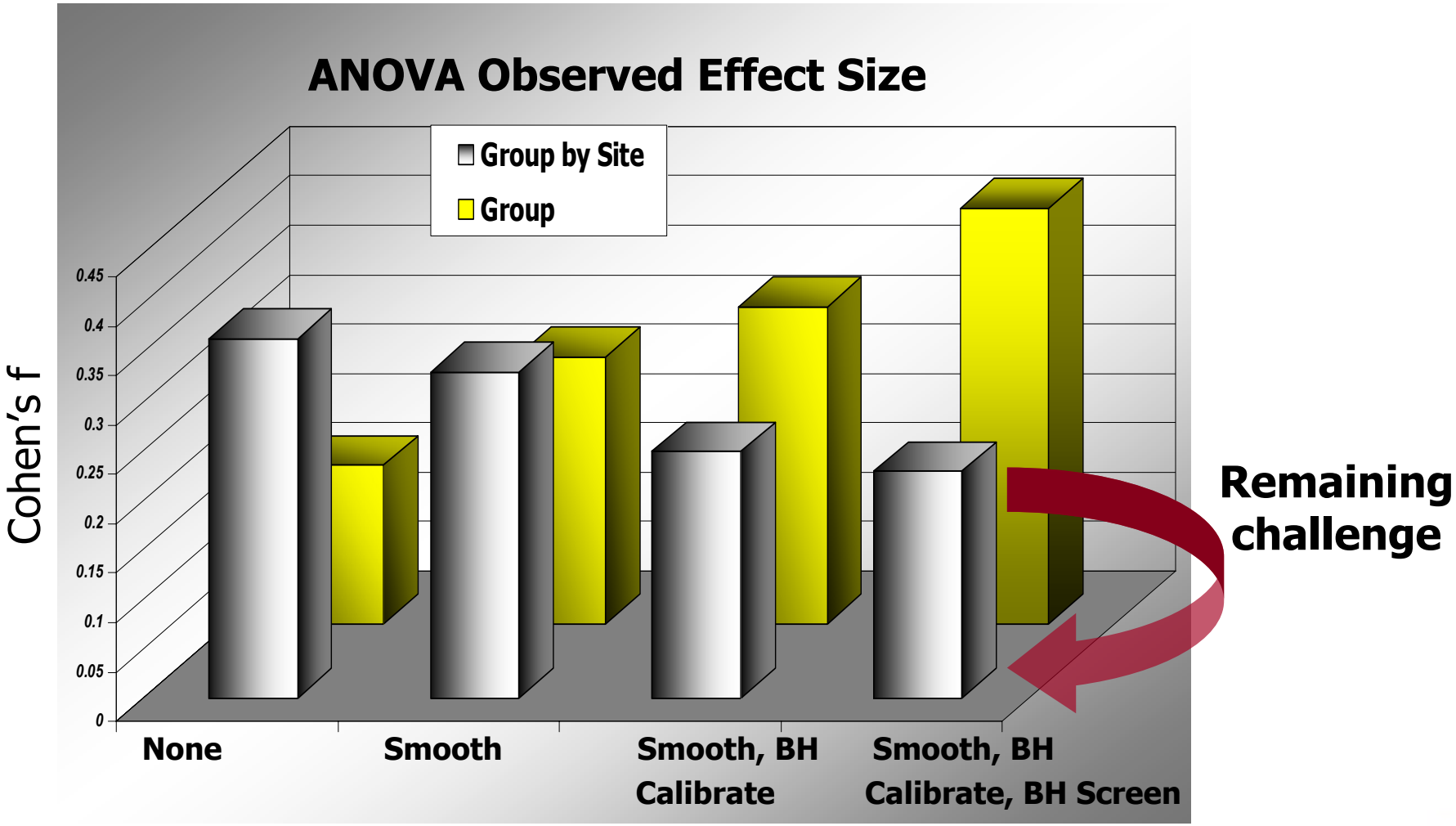
Impact of fBIRN Calibration Methods



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Biomarkers - Conclusion

- The establishment of reliable biomarkers necessitates understanding and overcoming sources of variability due to subject and site.

- Access to a common set of acquisition protocols, processing and analysis tools, and data sharing infrastructure increase the chances of success.

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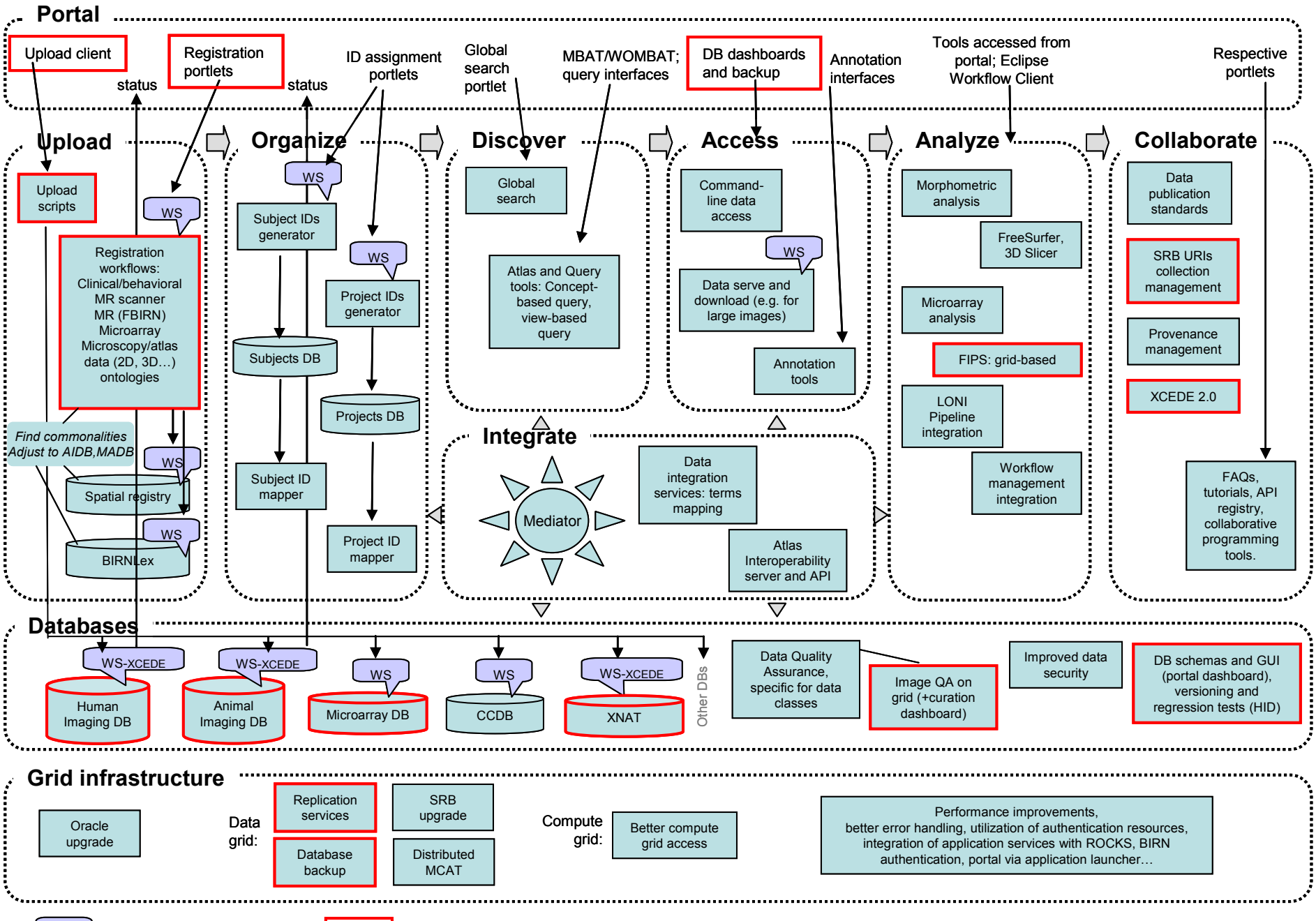
BIRN Roadmap



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