MICCAI 2008 – MIAMS Workshop
September 6, 2008

Effects of Z-Shift-Associated Gradient-Distortions on SIENA-Generated Measures of Brain Atrophy

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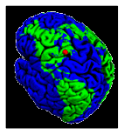
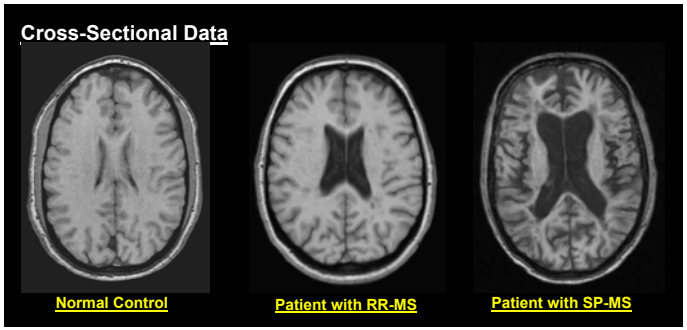


Brain Atrophy
- An Ongoing Process in Patients with Multiple Sclerosis (MS)

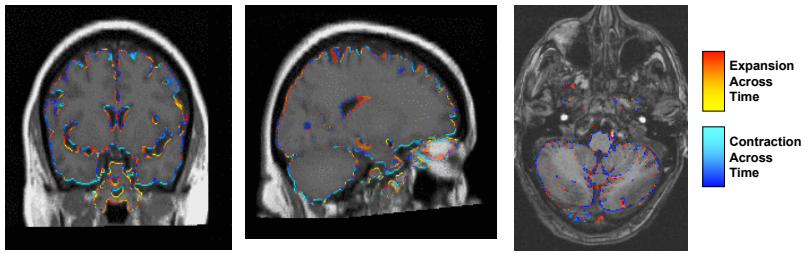
- Brain atrophy is evident in the relapsing-remitting (**RR**) phase of MS
- It is even more severe in the secondary-progressive (**SP**) stage
- Accordingly, precise and accurate measurement of brain atrophy is an important goal in understanding both:
  - The natural progression of patients with MS
  - How different treatment approaches can affect this natural progression



SIENA (Structural Image Evaluation, using Normalization, of Atrophy)
- Commonly-Used MRI-Based Measure of Brain Atrophy

- SIENA provides fully-automated estimates of percentage brain volume change (**PBVC**) between two appropriate MR images of the same subject (which are typically acquired at two different points in time)
  - These values represent the net sum of all brain surfaces that expand and contract across these two images
- SIENA values are highly accurate and largely independent of slice thickness (the initial validation studies finding a median absolute-error = 0.15%)
- A recent study found a median annual SIENA decrease of -0.61% in 147 treated patients with early RR-MS (Horakova, 2008)
  - For comparison, normal adults show annual decreases of about 0.1% to 0.3% (De Stefano, 2007)

SIENA-Calculated Regions of Expansion and Contraction across Time

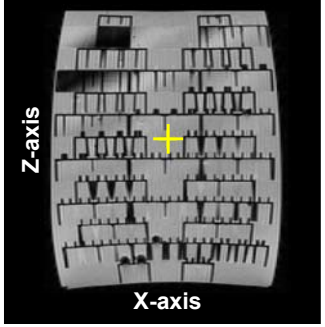


- Adapted from *http://www.fmrib.ox.ac.uk/analysis/research/siena/slideshow/index.html*

Potential Confounds
- Factors That Can Effect the MRI-Measurement of Brain Atrophy

- The precision and accuracy of SIENA can be affected by local-volume changes related to:
  1) **Non-Linear Gradient-Distortions (GD)**
     Typical of newer-generation MRI systems designed to have short bores and short gradient-rise-times; they result in "barrel-shaped" distortions that increase with distance from magnet-isocenter (indicated by the yellow crosshairs)

MRI Image of our Phantom
(which has perfectly straight lines, but APPEARS barrel-shaped)



Potential Confounds
- Factors That Can Effect the MRI-Measurement of Brain Atrophy

- The precision and accuracy of SIENA can be affected by local-volume changes related to a combination of:
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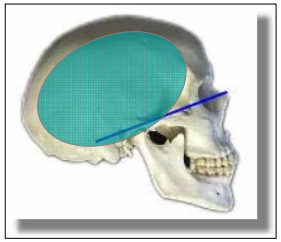
     Typical of newer-generation MRI systems designed to have short bores and short gradient-rise-times; they result in "barrel-shaped" distortions that increase with distance from magnet-isocenter
  2) **Inconsistent positioning of subjects within the scanner**
     Particularly along the long, Z-axis of the magnet
     (As we will see, if not controlled for, this is actually quite common)
  3) **Typical, canthomeatal (CM) alignment within the magnet**
     Which results in an individual's brain being centered several centimeters further into the magnet than isocenter (indicated by the blue line)

Canthomeatal Plane:
A plane passing through the junction of the upper and lower eyelids and the center of the ear canal.



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- Factors That Can Effect the MRI-Measurement of Brain Atrophy

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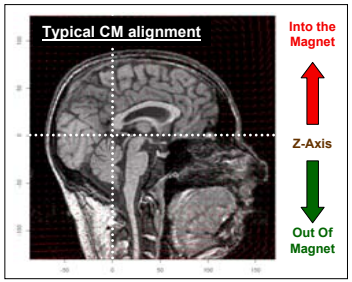
     Particularly along the long, Z-axis of the magnet
     (As we will see, if not controlled for, this is actually quite common)
  3) **Typical canthomeatal (CM) alignment within the magnet**
     Which results in an individual's cerebrum being centered several centimeters further into the magnet than isocenter
     (indicated by the blue line)

– **As a result of these three factors**
  - Z-shifts of several centimeters **into the magnet** result in the bulk of the brain moving even further away from isocenter
    - where it would experience **greater GD effects**
  - Z-shifts of similar extent **out of the magnet** result in the bulk of the brain moving closer towards isocenter
    - where it would experience **lesser effects of GD**



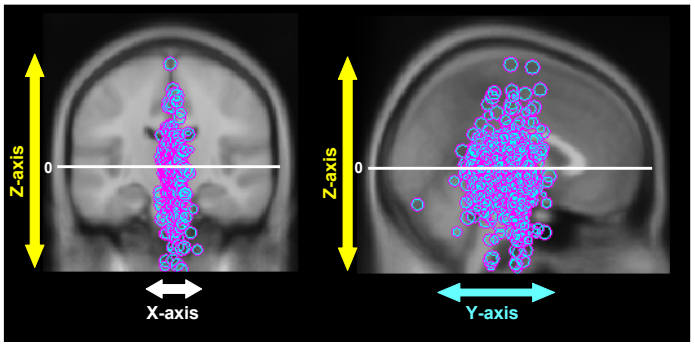
Setting The Context
- Outline of the Present Presentation

- Today we will examine four things:
  I - The extent of variability found in Z-positioning in a large, recent clinical-trial
  II - Our use of a novel MRI phantom to characterize and correct the GD-field associated with our scanner
  III - The effect of actual Z-shifts on SIENA values (both before and after correcting for GD)
  IV - Simulations examining what might be expected with a greater range of Z-shifts
- Please note that, because of the limited time available, I will be skipping most of the technical details of our study (BUT, these can be found in the conference proceedings)

Part I: A High-Degree of Variability in Z-Positioning Can Be Observed

What is the Expected Extent of Variability in Z-Positioning?
- Post-Hoc Analysis of a Recent Multicenter-Clinical-Trial

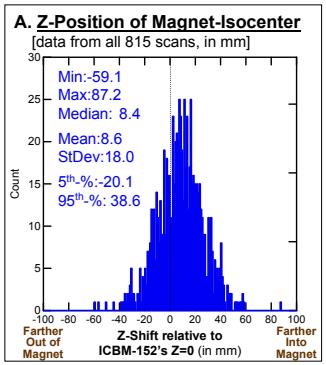
- We performed a post-hoc analysis of 815 typically-acquired T1-weighted MRI scans from a recent multicenter clinical trial
  - These data were acquired in a sample of 100 patients with MS (each with a Baseline Scan and up to 8 Follow-Up Scans over the course of 48 weeks)
- The blue circles show the anatomical location of the magnet-isocenter in each of these 815 scans superimposed on the ICBM-152 T1 image (ideally these should all be very close to one another: this is definitely not the case!)

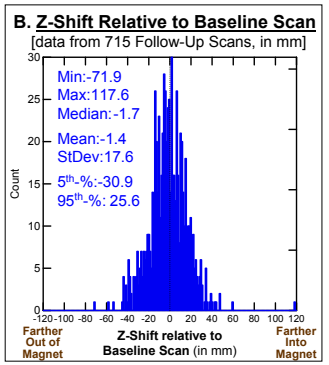


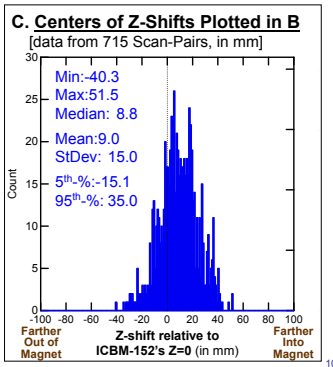
These data show:
- Very little variability in X-positioning
- Somewhat more variability in Y-positioning
- Tremendous variability in Z-positioning

What is the Expected Extent of Variability in Z-Positioning?
- Post-Hoc Analysis of a Recent Multicenter-Clinical-Trial

- With regards to the extent of Z-variability in these 815 scans:
  - **A**. The actual anatomic Z-location of isocenter ranged from ~6-cm further out of, and ~9-cm further into, the magnet (relative to Z=0 on the ICBM-152 image)
  - **B**. The degree of Z-shift relative to the Baseline Scan for each of the 715 Follow-Up scans ranged between about -7-cm and +12-cm
  - **C**. The Z-shift between these 715 Baseline-vs.-Follow-Up scan-pairs was centered upon a point that ranged between about 4-cm further out of, and 5-cm further into, the magnet
- These data suggest a relatively-high degree of variability in Z-positioning in these typically-acquired MRI scans: both across, and within, individuals







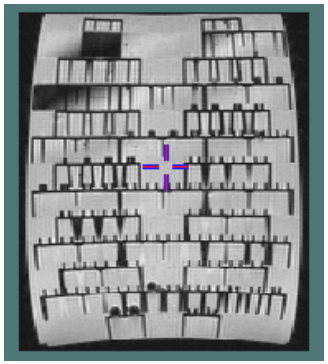
Part II: Our Use of a Novel MRI Phantom to Characterize Gradient-Related Geometric Distortions

Our Approach to Measuring and Correcting Such Geometric Distortions
- Uses a ®DUPLO-Based MRI Phantom

- ®duplo is a version of ®Lego that is eight times the size (twice the length) of the traditional Lego bricks
- The phantom is made of 125 bricks assembled in a regular pattern inside an 8-L plastic container (filled with a water solution of 0.15mM/l $MnCl_2$ and 2.8g/l NaCl)
  - As you can see, this is large enough to contain even a big-sized head (mine!)
- Such a phantom can easily and precisely be reproduced across multiple sites with minimal cost; it can also be customized for different acquisition parameters (*e.g.*, head-coil size, field of view, *etc.*)

MRI Acquisitions
- ®DUPLO-Based Phantom

- Three sets of global, T1-weighted scans of the Phantom were acquired on our 1.5T SIEMENS Sonata scanner
  (3D-FLASH acquisition: TR = 22 ms, TE = 10 ms, flip angle = 30°, sagittal partitions that were 1.5-mm thick, FOV = 250 mm with a phase of 100%, 256 x 256 matrix, 100% sampling, nominal number of slices = 110, 1 average, bandwidth = 70 Hz/Px, AP-direction phase-encoding)
  - One set was acquired **at magnet isocenter** (and shows typical "barrel distortion")
  - A second set was acquired **50-mm further-in**
  - A third set was acquired **50-mm further-out**

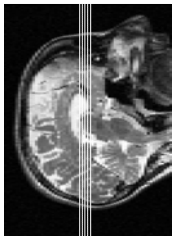


MRI Acquisitions
- Normal-Control (NC) Subjects

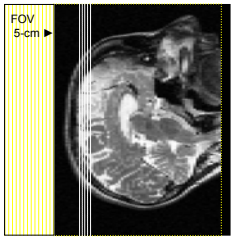
- Three sets of T1-weighted MRI data were also acquired in 9 NC subjects
  - Same scanner and same imaging parameters as the Phantom

Scan Session 1
Place subject in scanner and acquire two datasets:

CM Dataset
Canthomeatally-Aligned



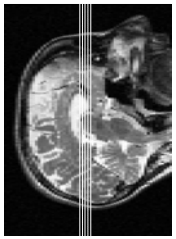
Z-50 Dataset
Scanner bed is moved 50-mm further out



Subject exits scanner

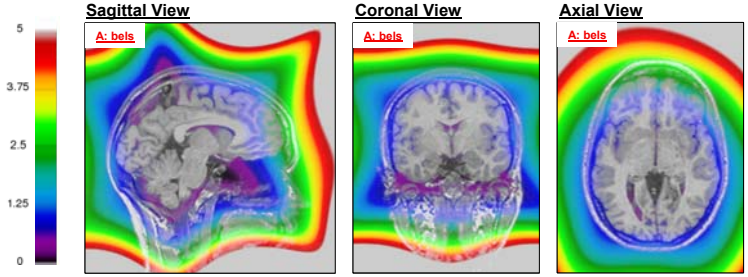
Scan Session 2 (on same day)
Subject back in scanner

Repos Dataset
"Best-Possible" Repositioning (Aligned with CM Dataset)

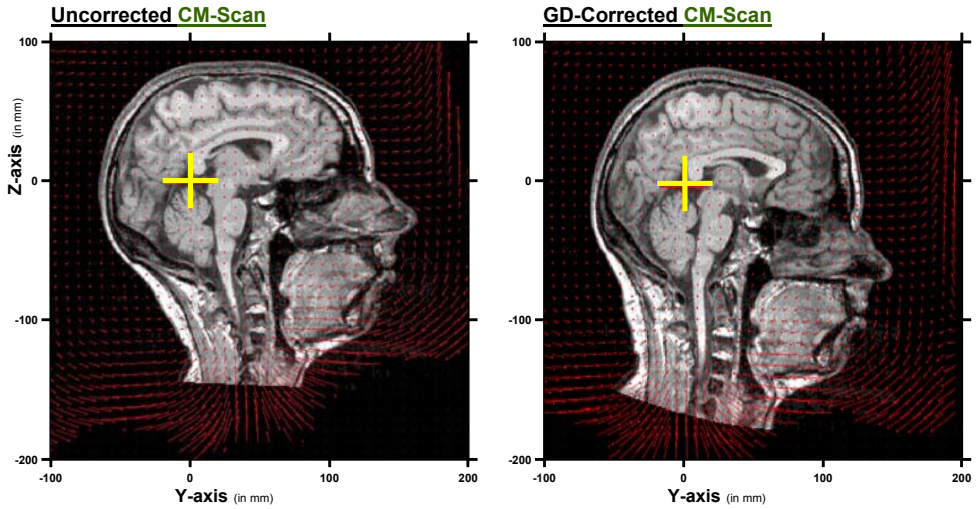


Characterizing the Gradient-Distortion (GD) Field
- Spherical Harmonic Approach

- Spherical harmonic expansion was used to characterize the GD-field associated with our particular scanner and T1-weighted acquisition
  - This method allowed us to map coordinates from a known "ideal" coordinate system (*i.e.*, that of our ®DUPLO-based phantom) to the imaging coordinate system of our scanner
- We used this approach to generate an estimate of our GD-field based on the three scans of our Phantom
  - This GD-field can be seen below, with the color scale representing the distance (in mm) that a voxel seems to move between it's "real" location and its "apparent" location on the MR image
  - Showing one of our subject's brains on the GD-field should give you a better idea of its dimensions



Our Approach to Correcting for Gradient-Distortion (GD)
- Apply the Inverse of the GD-Field



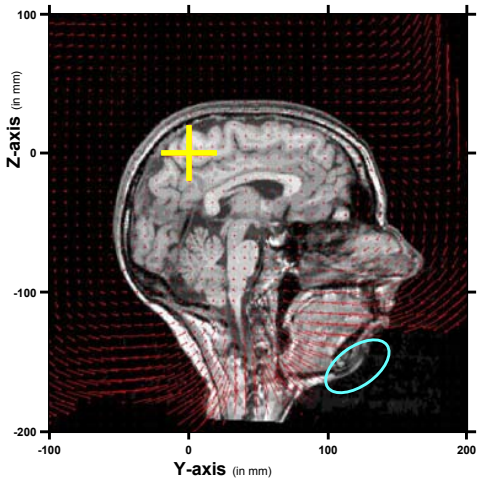
Yellow Cross:
Indicates the location of the magnet's isocenter

Red Vectors:
Indicate the GD-Field

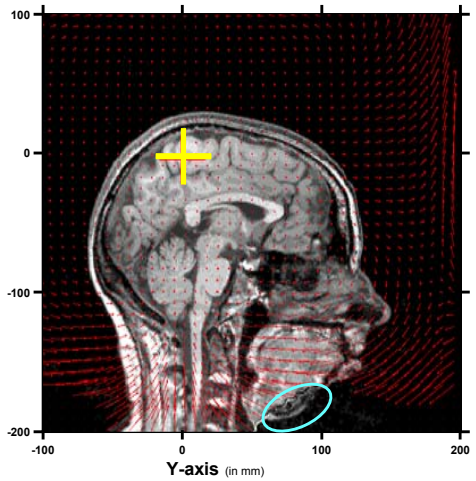
NB – GD-correction reduces the barrel-distortion that is seen in the uncorrected **CM Scan**

Our Approach to Correcting for Gradient-Distortion (GD)
- Apply the Inverse of the GD-Field

Uncorrected Z-50 Scan



GD-Corrected Z-50 Scan



Yellow Cross:
Indicates the location of the magnet's isocenter

Red Vectors:
Indicate the Gradient-Distortion Field

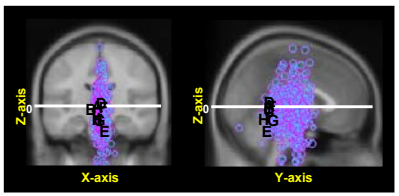
NB – GD-correction also reduces the barrel-distortion that is seen in the uncorrected **Z-50 Scan**

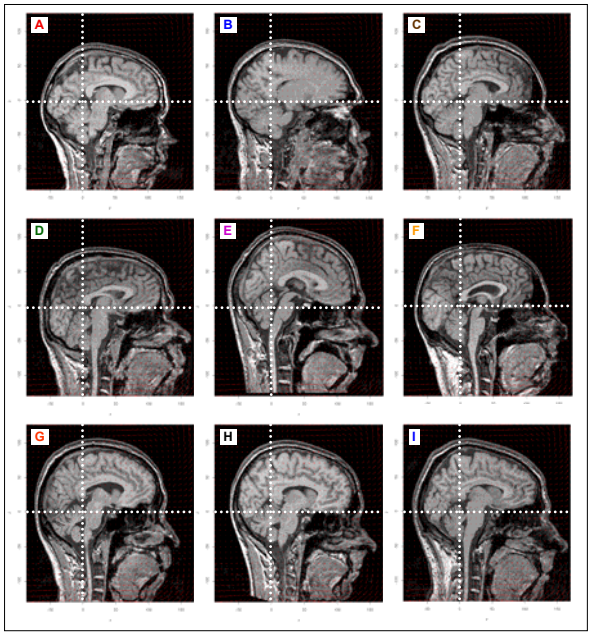
Note that the chin is not corrected because it lies outside the GD-Correction Field

Part III: Effect of Actual Z-Shifts on SIENA-Measured Brain Atrophy

T1 Images of Our 9 Subjects' CM Scans
- White Lines Indicate Magnet Isocenter Along the Z- and Y-Directions

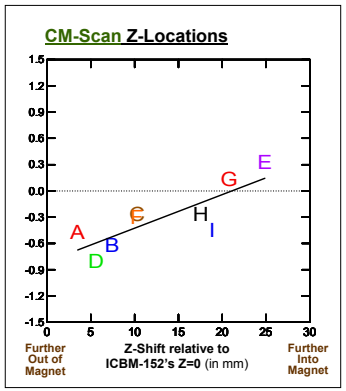
- The anatomical location of magnet-isocenter of the subjects' **CM Scans** is shown below (in black letters).
  - Although there is some variability in X- Y- and Z-positioning, it is much less than in the clinical-trial scans (the blue circles)

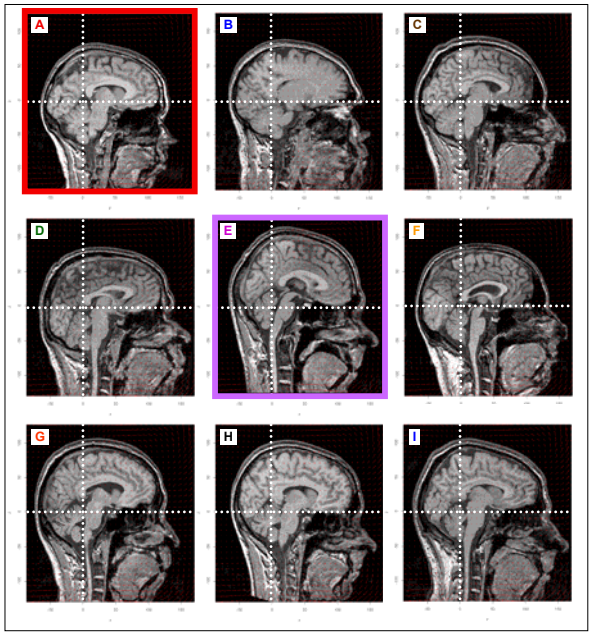




T1 Images of Our 9 Subjects' CM Scans
- White Lines Indicate Magnet Isocenter Along the Z- and Y-Directions

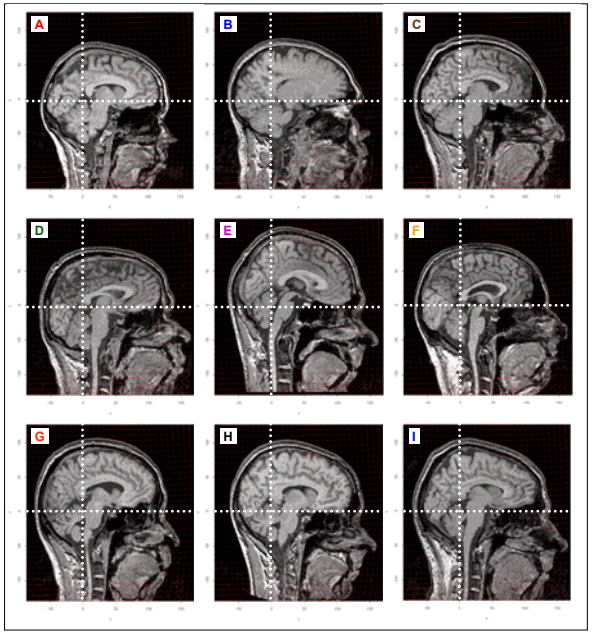
- The extent of Z-positioning variability in the subjects' **CM Scans** is plotted below
  - Note that there is a difference of ~2.5-cm in the Z-positioning of subjects **A** and **E**





T1 Images of Our 9 Subjects' CM Scans
- White Lines Indicate Magnet Isocenter Along the Z- and Y-Directions

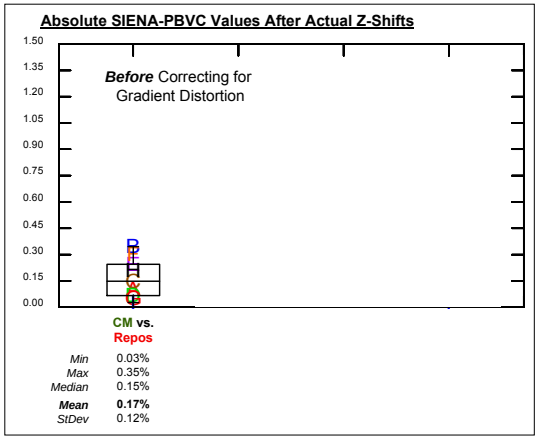
- Moving the scanner bed 50-mm out for the **Z-50 Scans** successfully resulted in a mean Z-shift of -49.2-mm relative to each subjects' **CM Scan** (range of -50.9 to -48.4)
- BUT, even with our attempt at "best-possible" repositioning for the **Repos-Scans**, there was a mean Z-shift of 4.3-mm relative to each subjects' **CM Scan** (range of -9.0 to 21.1)
  - **Accurate repositioning is tough!**
- We examined how these Z-shifts would result in apparent changes in SIENA values (even when no real biologically-related changes would have occurred)
- SIENA analyses were carried out both before, and after, the subjects' scans underwent GD-correction



Effect of Actual Z-Shifts on SIENA-Measures of Brain Atrophy
- Results from SIENA v2.5 (FMRIB Software Library (**FSL**) v4.0.3)

- **Before GD-Correction**
  - **CM vs. Repos**

"Best-possible" repositioning resulted in:
- A median absolute-error of about 0.15% (the degree of precision that was described in the original SIENA validation studies)
- A maximum absolute-error of 0.35%



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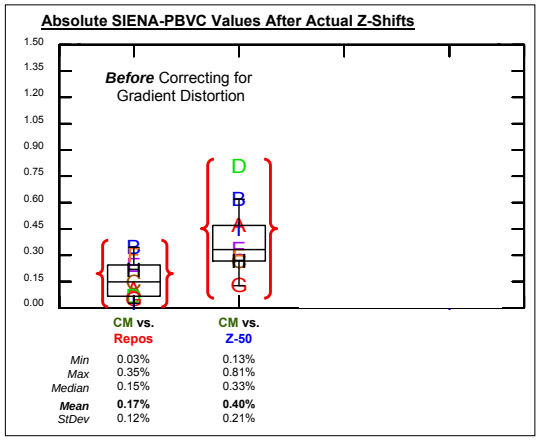
  - **CM vs. Z-50**

50-mm Z-shifts out of the magnet resulted in:
- A significantly-higher mean absolute-error of about 0.40% (versus 0.17% for "best-possible" repositioning, p=0.003)
- AND, a maximum-absolute-error of 0.81% (which is greater than the median annual-PBVC-value in patients with MS!)



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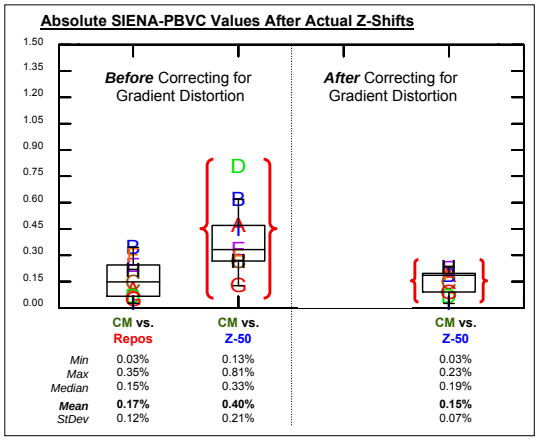
- **After GD-Correction**

The "apparent" brain volume changes associated with the **Z-50** shifts were reduced:
  - The mean absolute-error was reduced from 0.40% to 0.15% (p = 0.001); and it was no longer significantly different from that found after "best-possible" repositioning (*i.e.* uncorrected **CM** vs. **Repos**)



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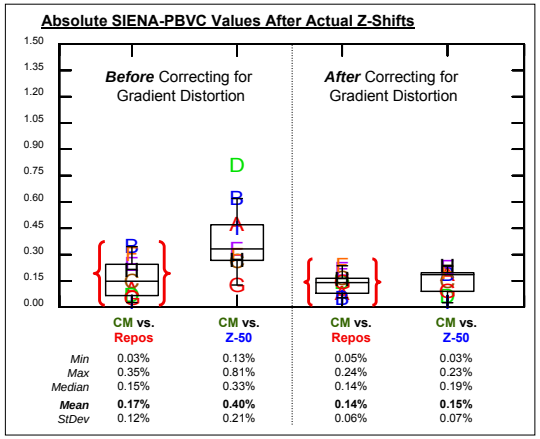
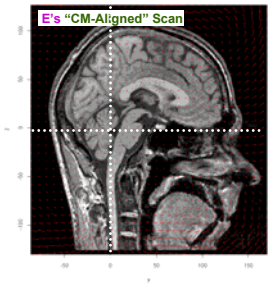
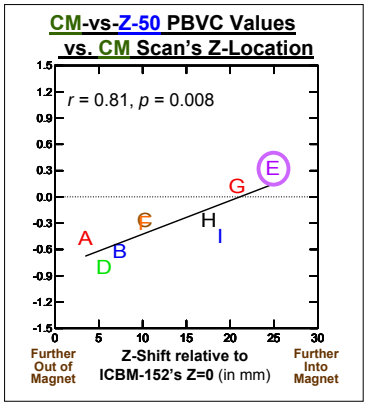
- **After GD-Correction**
  the "apparent" brain volume changes associated with the Z-50 shifts were reduced:
  - The mean absolute-error was reduced from 0.40% to 0.15% (p = 0.001) and was no longer significantly different from that found after "best-possible" repositioning (*i.e.* uncorrected CM vs. Repos)
- GD-correction also decreased the absolute-errors associated with our "best-possible" repositioning
  - But this was not statistically-significant (p = 0.969) - perhaps due to our small sample size



Effect of Actual Z-Shifts on SIENA-Measures of Brain Atrophy
- Relationship between PBVC values and Z-Location in the Magnet

- As expected, a positive relationship was found between
  (i) the degree of brain volume "change" induced by an actual Z-shift of 50-mm out of the magnet, and
  (ii) the Z-location of the subject's **CM Scan**
- For example:
  - Subject E's **CM Scan** was acquired with much of the brain farther away from isocenter (where it would appear as "atrophied" as a result of the GD it experienced there)
  - BUT, Subject E's **Z-50 Scan** was acquired with the brain 5-cm closer to isocenter (where it would experience less of this GD-related "atrophy")
  - As a result, there is an "apparent" increase in brain volume for this individual following a Z-shift of 50-mm out of the magnet



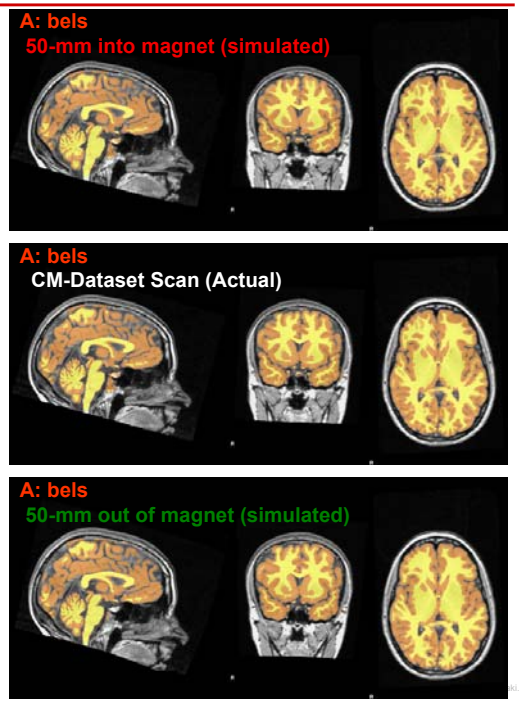


- This finding emphasizes the point that it is not simply a question of how much Z-shift occurs across two scans, **but also where this Z-shift is centered**

Part IV: Effects of Simulated Z-Shifts on SIENA-Measured Brain Atrophy

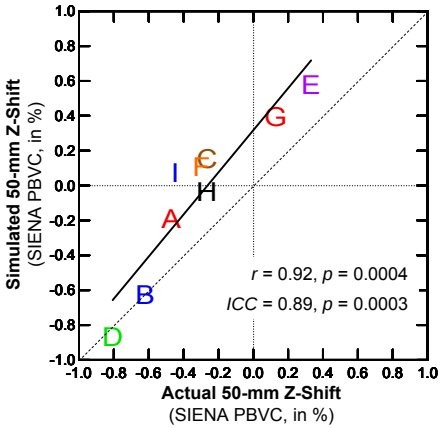
Effects of Simulated Z-Shifts on SIENA-Measures of Brain Atrophy
- Method

- For each subject, the effect of Z-shift was simulated in 5-mm steps from -50-mm to +50-mm:
  (i) The GD-correction field was applied to each subject's **CM Scan**
  (ii) This GD-corrected data was Z-shifted by the desired amount
  (iii) The GD-field was then applied to this Z-shifted data
- This procedure resulted in 21 sets of simulated data for each subject (as illustrated to right)
  - This allowed us to generate a series of SIENA comparisons examining the effect of a range of between-scan Z-shifts similar to that seen in the multicenter clinical-trial data (both in terms of their magnitude and the location around which they were centered)



Effects of Simulated Z-Shifts on SIENA-Measures of Brain Atrophy
- Validation

- **Evidence for the validity of this approach** is provided by the strong correspondence between SIENA values that resulted from an **actual Z-shift of 50-mm out of the magnet** and a **simulated Z-shift of 50-mm out of the magnet**
  - These two sets of SIENA values were highly correlated (r = 0.92, p = 0.0004)
  - And, they showed a high degree of absolute-agreement [ICC = 0.89, p = 0.0003]

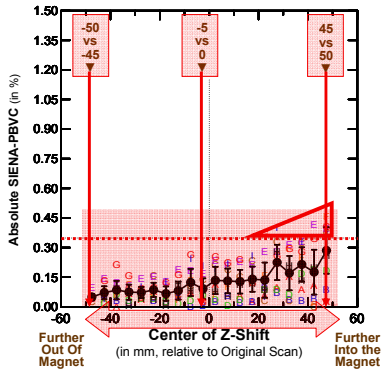


Effects of Simulated Z-Shifts on SIENA-Measures of Brain Atrophy
- Results: Depend on the Magnitude and the Center of the Z-Shift

- **Differences of 5-mm**
  (*e.g.*, -50-mm vs. -45-mm)
  - Resulted in only very-small absolute-errors throughout the range of simulations

- **How the Data is Plotted**
  - Examples of the pair of simulated Z-shifts being compared are shown at the top
  - The points around which the pair of simulated Z-shifts are centered are plotted along the x-axis
  - A horizontal line signifies the maximum SIENA value of 0.35% that was seen in these 9 NC subjects following "best-possible" repositioning
  - For each center point, the absolute value for each individual is shown, as is the overall mean (± 95% confidence interval)
  - A red polygon outlines those simulations that resulted in absolute values greater than 0.35%

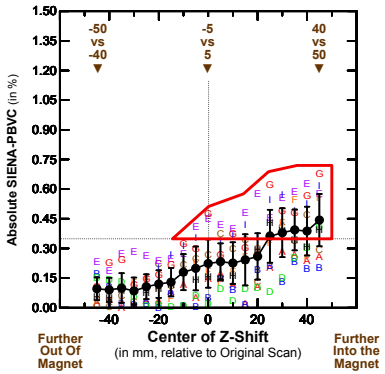
A. 5-mm Z-Shift Differences



Effects of Simulated Z-Shifts on SIENA-Measures of Brain Atrophy
- Results: Depend on the Magnitude and the Center of the Z-Shift

- Differences of 5-mm
  (*e.g.*, -50-mm vs. -45-mm)
  - Resulted in only very-small absolute-errors throughout the range of simulations
- **Differences of 10-mm**
  - Resulted in larger errors as the simulated Z-shifts were centered further into the magnet

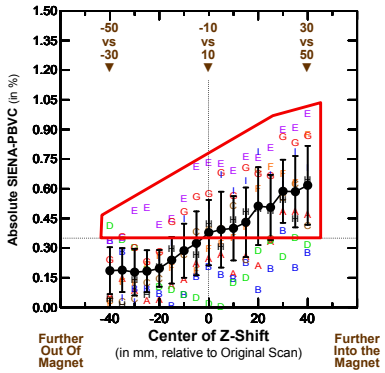
B. 10-mm Z-Shift Differences



Effects of Simulated Z-Shifts on SIENA-Measures of Brain Atrophy
- Results: Depend on the Magnitude and the Center of the Z-Shift

- Differences of 5-mm
  (*e.g.*, -50-mm vs. -45-mm)
  - Resulted in only very-small absolute-errors throughout the range of simulations
- Differences of 10-mm
  - Resulted in larger errors as the simulated Z-shifts were centered further into the magnet
- **Differences of 20-mm to 40-mm**
  - Also resulted in larger errors when the simulated Z-shifts were centered further into the magnet: BUT these errors become progressively greater in magnitude, and are seen with Z-shifts centered even less far into the magnet as the differences increase from **20-mm**

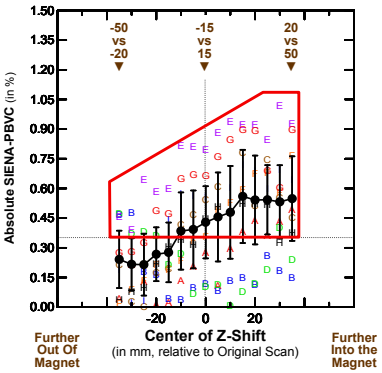
C. 20-mm Z-Shift Differences



Effects of Simulated Z-Shifts on SIENA-Measures of Brain Atrophy
- Results: Depend on the Magnitude and the Center of the Z-Shift

- **Differences of 5-mm**
  (*e.g.*, -50-mm vs. -45-mm)
  - Resulted in only very-small absolute-errors throughout the range of simulations
- **Differences of 10-mm**
  - Resulted in larger errors as the simulated Z-shifts were centered further into the magnet
- **Differences of 20-mm to 40-mm**
  - Also resulted in larger errors when the simulated Z-shifts were centered further into the magnet: BUT these errors become progressively greater in magnitude, and are seen with Z-shifts centered even less far into the magnet as the differences increase from 20-mm to **30-mm**

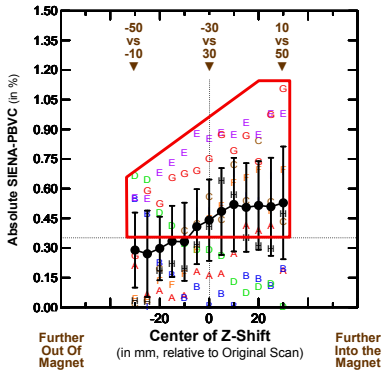
D. 30-mm Z-Shift Differences



Effects of Simulated Z-Shifts on SIENA-Measures of Brain Atrophy
- Results: Depend on the Magnitude and the Center of the Z-Shift

- **Differences of 5-mm**
  (*e.g.*, -50-mm vs. -45-mm)
  - Resulted in only very-small absolute-errors throughout the range of simulations
- **Differences of 10-mm**
  - Resulted in larger errors as the simulated Z-shifts were centered further into the magnet
- **Differences of 20-mm to 40-mm**
  - Also resulted in larger errors when the simulated Z-shifts were centered further into the magnet: BUT these errors become progressively greater in magnitude, and are seen with Z-shifts centered even less far into the magnet as the differences increase from 20-mm to 30-mm to **40-mm**

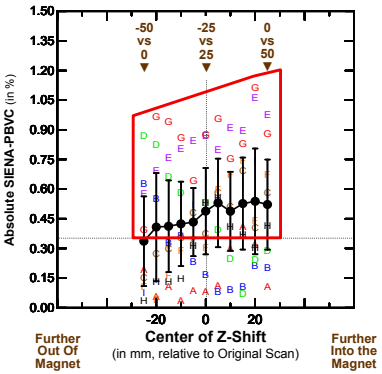
E. 40-mm Z-Shift Differences



Effects of Simulated Z-Shifts on SIENA-Measures of Brain Atrophy
- Results: Depend on the Magnitude and the Center of the Z-Shift

- **Differences of 5-mm**
  (*e.g.*, -50-mm vs. -45-mm)
  - Resulted in only very-small absolute-errors throughout the range of simulations
- **Differences of 10-mm**
  - Resulted in larger errors as the simulated Z-shifts were centered further into the magnet
- **Differences of 20-mm to 40-mm**
  - Also resulted in larger errors when the simulated Z-shifts were centered further into the magnet: BUT these errors become progressively greater in magnitude, and are seen with Z-shifts centered even less far into the magnet as the differences increase from 20-mm to 30-mm to 40-mm
- **Differences of 50-mm**
  - Consistently resulted in substantial errors in most subjects throughout the entire range of simulations

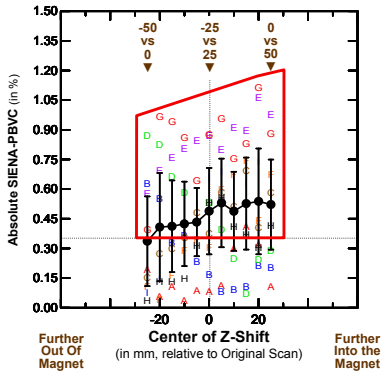
F. 50-mm Z-Shift Differences



Effects of Simulated Z-Shifts on SIENA-Measures of Brain Atrophy
- Results: Depend on the Magnitude and the Center of the Z-Shift

- **Differences of 5-mm**
  (*e.g.*, -50-mm vs. -45-mm)
  - Resulted in only very-small absolute-errors throughout the range of simulations
- **Differences of 10-mm**
  - Resulted in larger errors as the simulated Z-shifts were centered further into the magnet
- **Differences of 20-mm to 40-mm**
  - Also resulted in larger errors when the simulated Z-shifts were centered further into the magnet: BUT these errors become progressively greater in magnitude, and are seen with Z-shifts centered even less far into the magnet as the differences increase from 20-mm to 30-mm to 40-mm
- **Differences of 50-mm**
  - Consistently resulted in substantial errors in most subjects throughout the entire range of simulations

F. 50-mm Z-Shift Differences



- **Together, these findings are consistent with the notion of a "sweet spot" near magnet-isocenter**:
  - Within this sweet spot, MRI measures of volume and volume-change can be generated quite reliably
  - BUT, outside of this sweet spot, Z-shift-related GD can affect the accuracy of such measures

Discussion

Effect of Z-Shifts on SIENA-Measures of Brain Atrophy
- Summary of the Present Findings

- In summary, we have shown that:
  - If not specifically controlled for, inconsistent MRI positioning of subjects is actually quite common: particularly along the Z-axis
  - If not corrected for, the GD-effects associated with Z-shifts of even a few centimeters can significantly decrease the accuracy of SIENA-generated measures of brain atrophy
  - These negative effects seem to increase in magnitude as either:
    - The **distance from magnet-isocenter** of the brains increases
    - The **distance between the brains** increases
  - These confounding GD-effects can be reduced *post hoc* with the use of appropriately-generated correction fields
    - In our case, this was successfully created using a novel Phantom that is:
      - relatively-inexpensive to build,
      - easily-reproduced, and
      - highly-customizable

Effect of Z-Shifts on SIENA-Measures of Brain Atrophy
- Implications of the Present Findings

- It is important to note that the exact pattern of our findings are specific to our scanner and acquisition sequence
- Nevertheless, the overall pattern of these findings, and their implications, can be generalized to all MRI-derived metrics of brain volume and atrophy:
  - In order to increase the potential validity and reliability of such metrics, the effect of Z-shift-associated GD should be avoided, or accounted for
    - *E.g.*, the accuracy and precision of brain-atrophy estimates can be increased by:
      (i) Careful and consistent alignment to magnet-isocenter, and
      (ii) Correcting for the observed effects of GD
  - Importantly, this should lead to increased statistical power in studies aimed at understanding the natural progression and the effective treatment of disorders such as MS

Finally
- Many Thanks To the People Involved In This Project

- **MRS Lab**
  **Doug Arnold*
  Alexandre Carmel-Veilleux
  Elias Gedamu
  Elinor Tobman
  Jacqueline Chen
  Mishkin Derakhshan
  **Simon Francis*
  **Sridar Narayanan*
- **Image Processing Lab**
  Louis Collins
  **Vladimir Fonov*
- **MR Neuroimaging Lab**
  Bruce Pike
  Ives Levesque
- **McConnell Brain Imaging Centre**
  Andre Cormier
  David Costa
  Louis Marcotte
  Ron Lopez
- **All Of My Test Subjects**

Thank you for your attention!

Any questions?

"Always the beautiful answer who asks a more beautiful question"
e.e. cummings, Collected Poems (1963)