MRI Techniques in Studies of Gulf War Veterans

Further analyses of the white and gray matter

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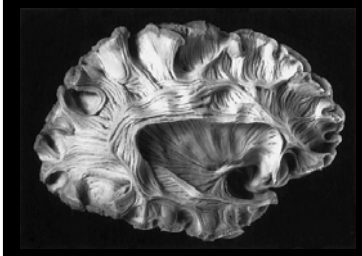
Gulf War illness

- Multi-symptom illness
  - Somatic complaints
  - Nonspecific neurological symptoms
  - Overlap with individual symptoms found in the general population
  - 25 to 30% of veterans that served in the gulf war have been affected by this syndrome
- Limited knowledge of etiology/neuropathology

Why focus on the white matter

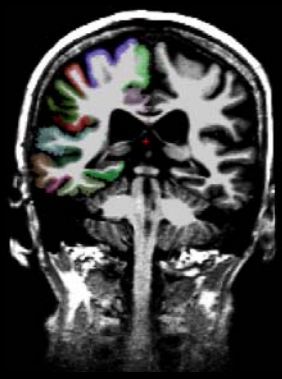


- White matter often the forgotten tissue
  - Susceptible to the effects of toxins
  - Central component to the changes seen in the process of normal aging
- Typical Gulf War illness symptoms include:
  - Fatigue
  - Headaches
  - Difficulties concentrating
- Features are consistent with those seen in individuals with disorders involving the white matter of the brain
  - Multiple sclerosis
  - Diffuse axonal injury

Imaging Techniques

- Advantages
  - Minimally invasive
  - Provide information about structure, function etc *in vivo.*
  - Potential for identifying a disease state and following the course of the disease and potential interventions.
    - Example = Multiple Sclerosis
  - Widely available
  - Tools of the processing of images are continually being developed and made available
    - BIRN grant
    - SPM
    - FSL
  - Images and computerized which fosters sharing and re-analysis.

What is Post Processing



–Technique used for quantifying information from the original MRI scan

- Why use post processing techniques?
  –Allows for quantification

–Best means of predicting Alzheimer's disease today come from the combination of psychometrics and MRI base quantification

Types of post processing procedures

Manual tracing
- - requires a skilled operator
- - labor intensive
- + high anatomic accuracy
- + can be done on virtually all types of images

Semi-automated procedures
- - uncertain anatomic accuracy
- - requires computer equipment and expertise
- + highly reproducible
- + requires attention to scan parameters

Fully-automated procedures
- -sensitive to image artifacts
- -not fully viable yet for all images
- +standard for processing some more recent image modalities
- +most reproducible and objective form of processing

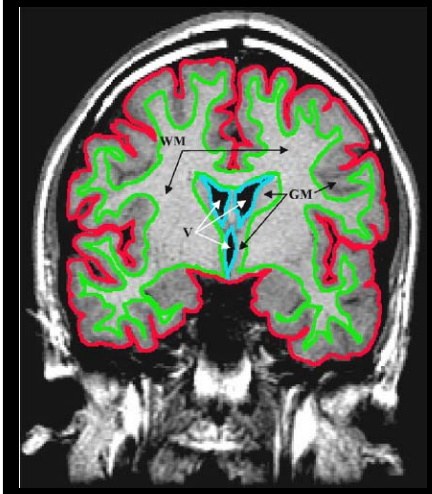
Initial Study of White Matter

Heaton et al, 2007

- Subjects
  - 13 sarin/cyclosarin exposed veterans
  - 13 sarin/cyclosarin unexposed veterans
- MRI study acquired on a GE 1.5T imager
  - Localizer
  - Dual Echo scan
  - T1 weighted SPGR
    - Coronal acquisition
    - 1.5 mm slice thickness
- Images post-processed using a semi-automated system that required user input and oversight.
  - MRX
  - Surgical Planning lab at BWH.

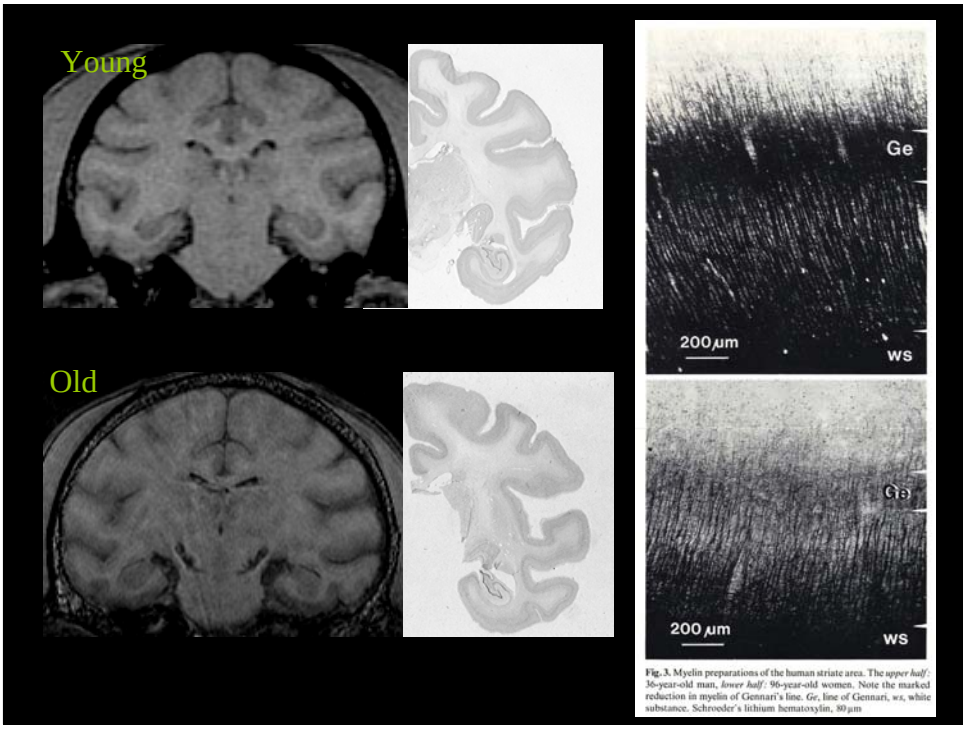
Initial Study of White Matter

Heaton et al, 2007



Single channel segmentation

- Measures:
  - Gray Matter
  - White Matter
  - CSF space (not including LVs)
  - Right Lateral Ventricle
  - Left Lateral Ventricle
- High Intra-rater reliability
- Results:
  - No overall differences between the unexposed and exposed subjects
  - 0.1 mg min/m^3 exposure level was associated with a 4.6% smaller WM volume in exposed subjects
  - 0.1 mg min/m^3 exposure level was associated with a 0.11 increase in the size of the right LV and a 0.13% increase in the size of the left LV in exposed subjects



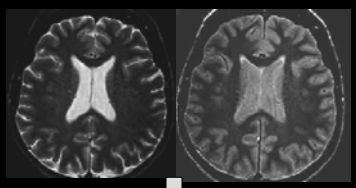
Further Studies of the WM - Segmentation

- Symptom groups (high vs low) as a surrogate marker
  - Based on 20 item survey given immediately upon return from active duty
  - 34 item survey given at the time of this study
    - Subjects were asked to rate symptoms only present post-deployment
- Subjects = 54
  - 19 originally reporting high symptoms
  - 35 originally reporting low symptoms
  - 22/32 at the time of this study
- MRI scanning conducted on a 3.0T Philips Imager using a phase array head coil
  - 3D scout/localizer & Sense reference scan
  - T1 weighted ADNI derived MPRAGE sequence
  - T2/PD weighted ADNI derived Double TSE sequence
    - Axial acquisition
    - 3.0 mm slice thickness
  - 3D FLAIR sequence
  - Diffusion Tensor Sequence
- T2/PD images processed using software developed to detect known pathology in MS subjects (TDS+)

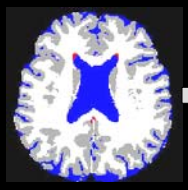
Segmentation Process

TDS+ Dual channel segmentation

Dual Echo or Double TSE



Automatic ICC generation, manual correction



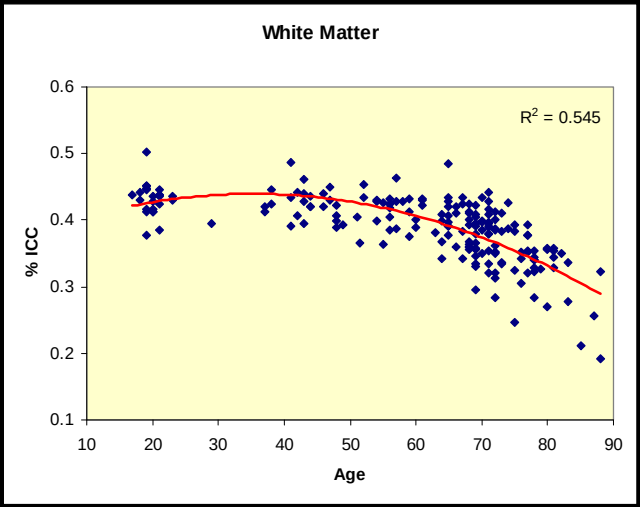
CSF, WMSA, WM, GM, ICC

Template Driven Segmentation

Partial Volume Error Correction

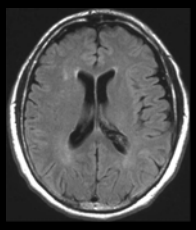
Guttmann et al

Cross Sectional Studies of Normal Aging

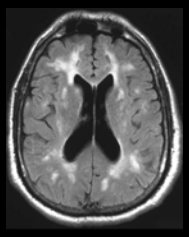


Spatial Distribution of WMSA

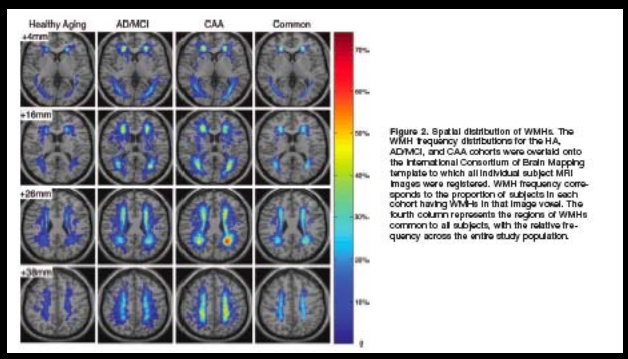
HA



CAA



FLAIR



Holland et al., Stroke 2008

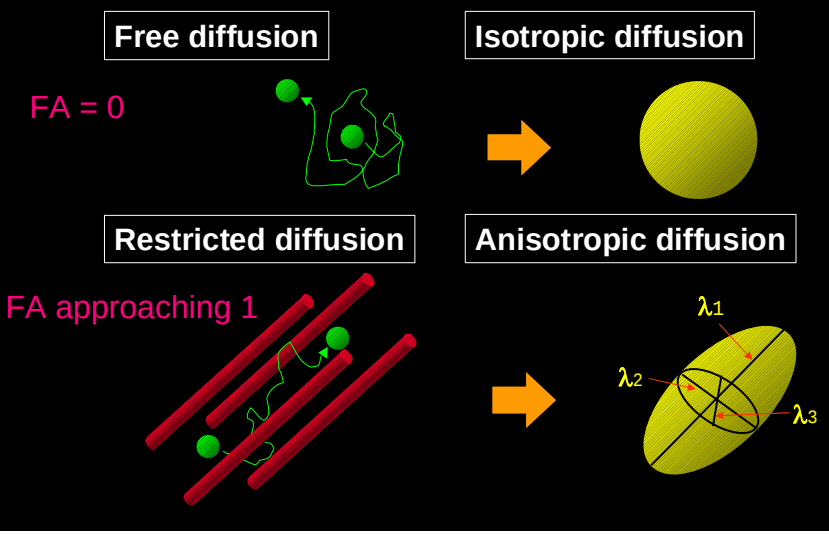
White Matter Segmentation Results

- Logistic Analyses
  - Controlling for age, sex and handedness
  - Odds ratios used to determine if MRI outcome measures (wm, wmsa, gm) could predict membership in the high symptom group
  - Data transformed to z-scores
- Results (original symptom groups):
  - White matter 2.45 p = 0.03 95% CI = 1.079-5.560
  - WMSA 0.69 p = 0.29
  - Gray matter 1.88 p = 0.15
  - CSF 1.30 p = 0.45
- Results (current symptom groups):
  - White matter 2.27 p = 0.06 95% CI = 0.942-5.457

White Matter Segmentation Summary

- Findings support the notion that differences in the white matter are a feature of subjects reporting high symptoms throughout the duration of the post-deployment period
- WMSA appear not to be a meaningful feature in our high symptom group
  - Common feature of some neurological disorders of the white matter
  - Multiple sclerosis
  - ? Alzheimer's disease
  - Vascular dementia
- What is the nature of the white matter change?
  - Explore using diffusion tensor imaging

In vivo labeling of axonal fibers using Diffusion Tensor Imaging (DTI)

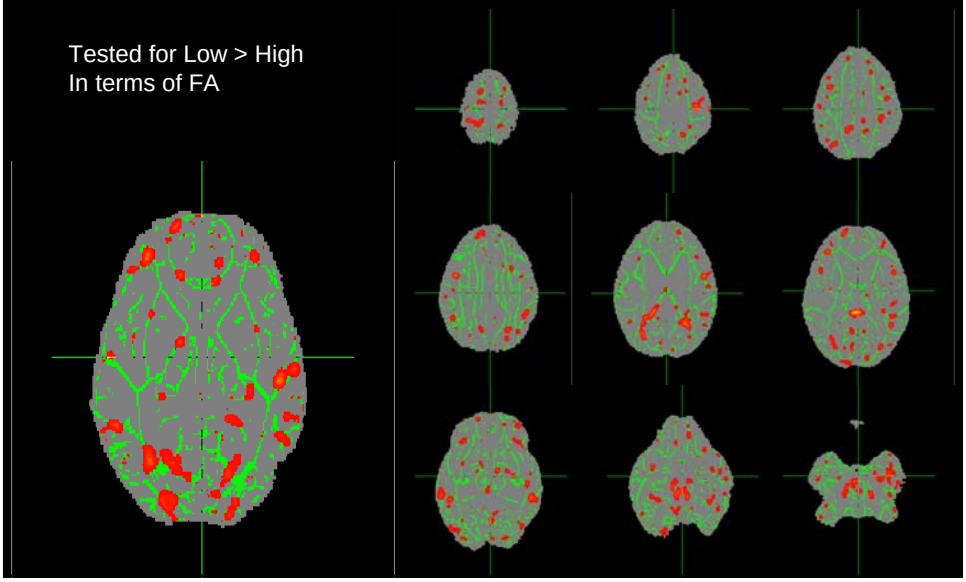


Further Studies of the White Matter - DTI

- MRI scanning conducted on a 3.0T Philips Imager using a phase array head coil
  - Diffusion Tensor Imaging (DTI) Sequence
    - Voxel size = 2 x 2 x 2 mm
    - Tensor directions = 15
    - Averaged three acquisitions to enhance S/N
- DTI data set processed using FSL software
  - (www.fmrib.ox.ac.uk/fsl/)
  - FDT package to create FA maps
  - TBSS used to make comparisons
  - Results portrayed visually

White Matter - DTI results

Tested for Low > High
In terms of FA



White Matter DTI Summary

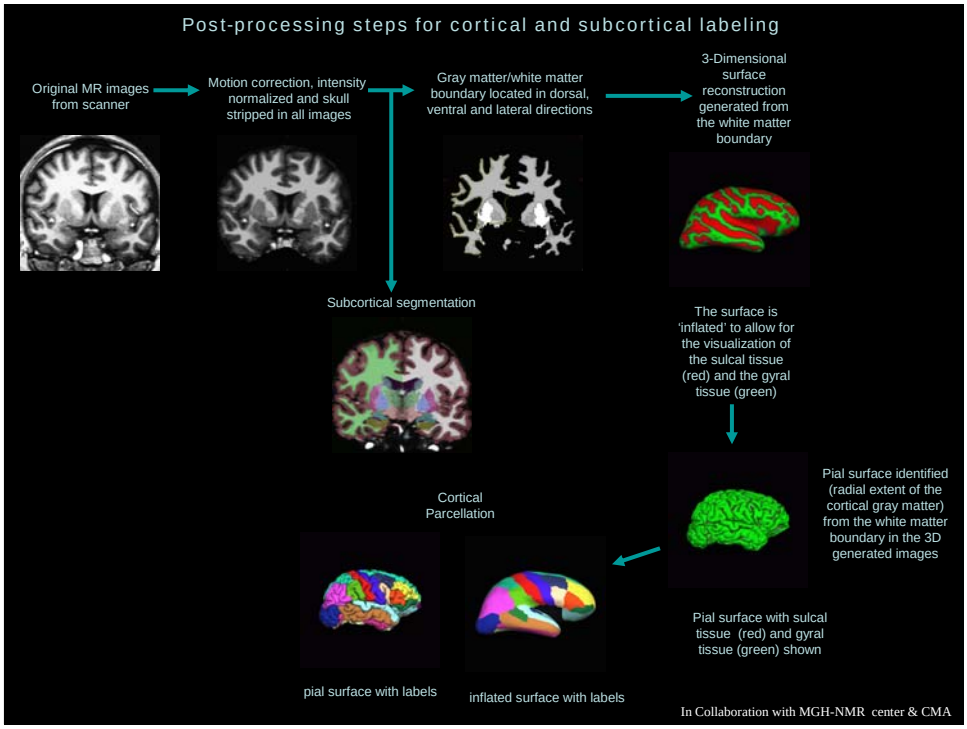
- Findings continue to support the notion that differences in the white matter are a feature of subjects reporting high symptoms throughout the duration of the post-deployment period
- Differences appear to be found throughout the white matter without focus on any particular pathway or tract
  - Regions of FA differences appear to represent differences in structural integrity of the white matter
  - Not foci of edema or ischemia

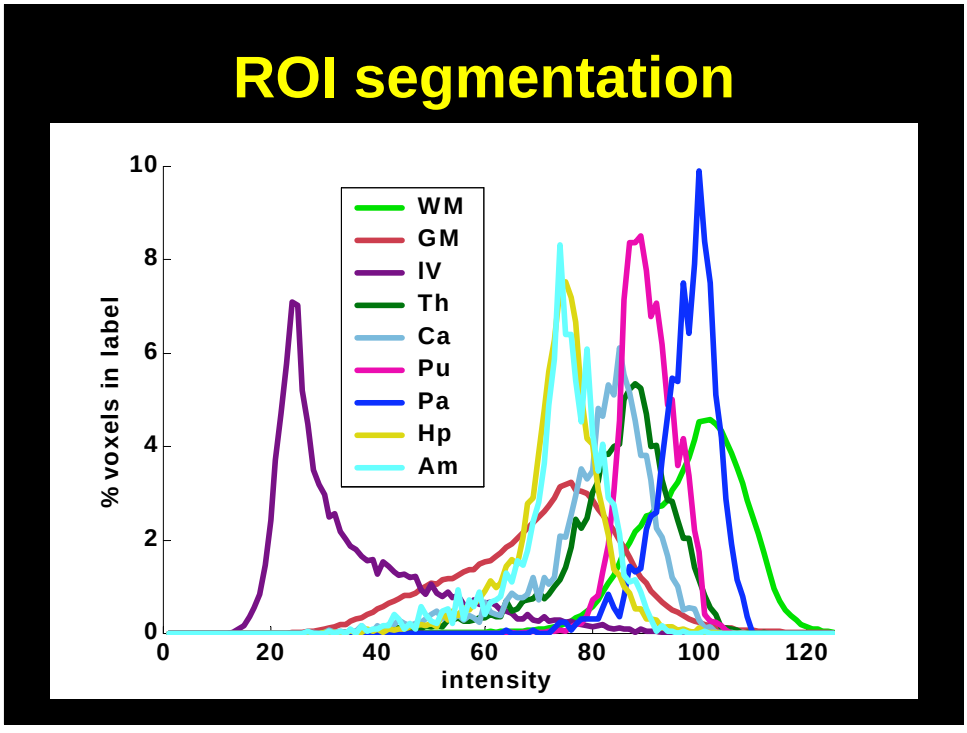
Do these ubiquitous white matter differences also reflect global gray matter differences between high and low symptom groups?

Studies of the Gray Matter - Morphometry

Exploratory analyses - not hypothesis driven

- Explore whether meaningful differences exist in the gray matter between high and low symptom groups
- MRI scanning conducted on a 3.0T Philips Imager using a phase array head coil
  - T1 weighted ADNI derived MPRAGE sequence
    - Sagittal acquisition
    - 170 slices at 1.2mm slice thickness
    - Scanner distortion and S/N tracked as part of the ADNI project
    - Sequence integrity re-established following all upgrades and service
- Images processed using Freesurfer probabilistic mapping approach to ROIs (surfer.nmr.mgh.harvard.edu)
  - Conversion to 1 x 1 x 1 voxels
  - N3 normalization
  - Subcortical segmentation
  - Cortical parcelation use the Desikan/Killiany Atlas
  - Outcome measures expressed as thickness, surface area and volume

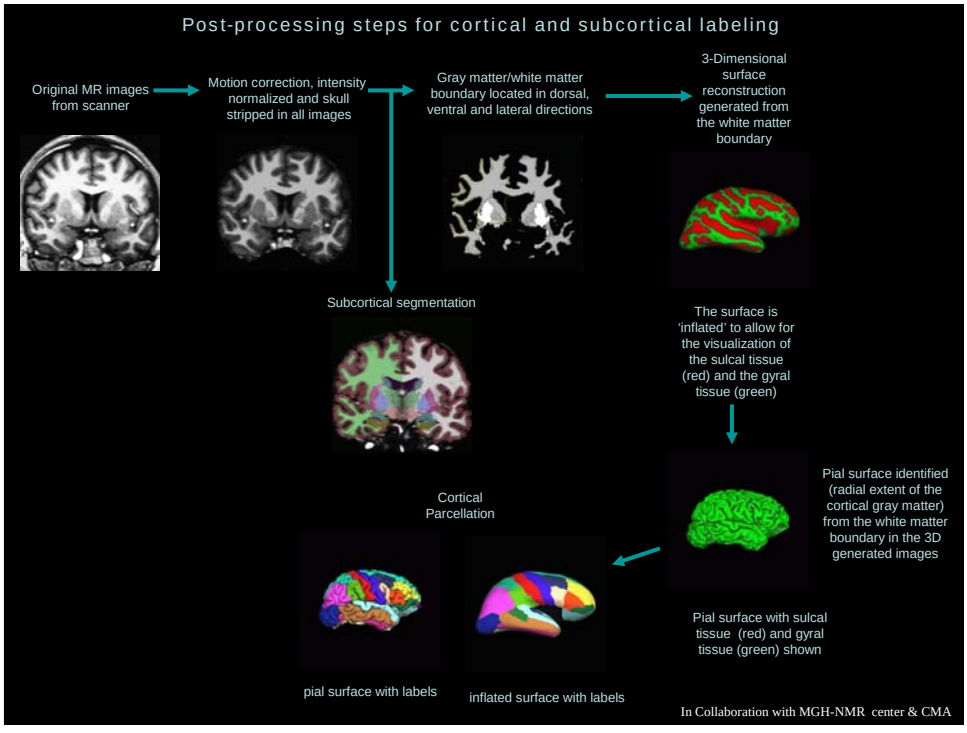

Post-processing steps for cortical and subcortical labeling
Original MR images from scanner
Motion correction, intensity normalized and skull stripped in all images
Gray matter/white matter boundary located in dorsal, ventral and lateral directions
3-Dimensional surface reconstruction generated from the white matter boundary
Subcortical segmentation
The surface is 'inflated' to allow for the visualization of the sulcal tissue (red) and the gyral tissue (green)
Pial surface identified (radial extent of the cortical gray matter) from the white matter boundary in the 3D generated images
Cortical Parcellation
Pial surface with sulcal tissue (red) and gyral tissue (green) shown
pial surface with labels
inflated surface with labels
In Collaboration with MGH-NMR center & CMA

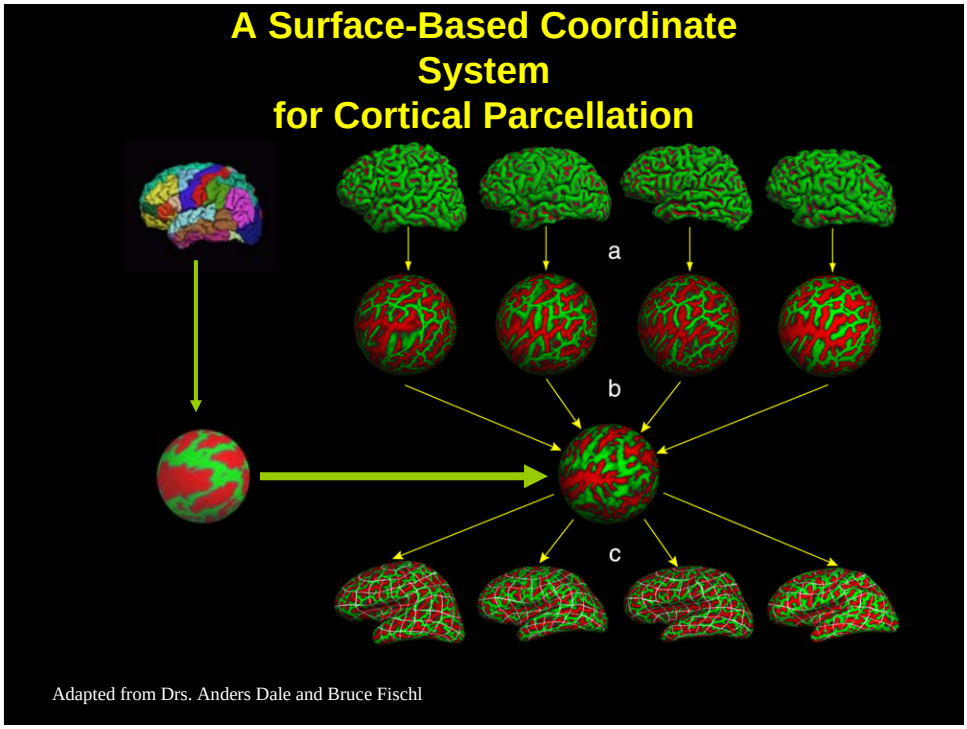

ROI segmentation
% voxels in label
intensity
WM
GM
IV
Th
Ca
Pu
Pa
Hp
Am
0
2
4
6
8
10
0
20
40
60
80
100
120

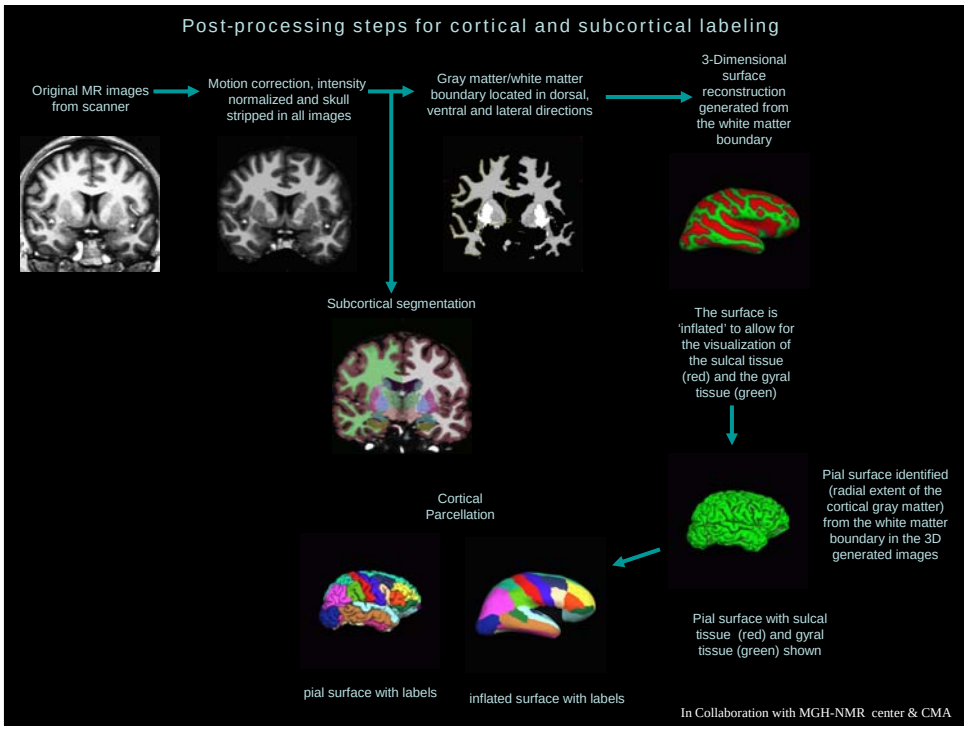
Segmentation: Gibbs Priors

Preliminary Segmentation

Final Segmentation




A Surface-Based Coordinate System for Cortical Parcellation
a
b
c
Adapted from Drs. Anders Dale and Bruce Fischl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Studies of the Gray Matter - Morphometry

Exploratory analyses - not hypothesis driven

- Logistic Analyses using volume as the dependent measure
  - Looking at current symptom groups
  - Controlling for age, sex and handedness
  - Odds ratios used to determine if MRI outcome measures could predict membership in the current high symptom group
  - Data transformed to z-scores and expressed as % TIV

Region	Left	Right	Region	Left	Right
STS	1.52	1.09	PostCing	0.72	1.15
CANTCing	0.64	2.63	Precent	0.97	1.41
CMidFront	0.95	1.02	Precuneus	0.92	1.45
Cuneus	0.81	0.87	RAntCing	1.14	1.75
Ento	1.37	1.52	RMidFrnt	0.80	1.28
Fusif	2.94	1.15	SupFrnt	0.97	0.75
InfPar	1.08	1.43	SupPar	0.75	0.81
InfTemp	1.64	1.59	SupTemp	1.05	1.64
IstCing	0.90	1.05	SupMarg	1.04	1.28
Loccip	1.20	1.12	FrntPol	0.86	0.73
LOrbFrnt	1.39	1.52	TempPol	1.23	1.08
Lingual	0.96	0.92	TransTemp	0.93	1.89
MOrbFront	1.02	0.96	LatVent	1.17	1.14
MidTemp	0.74	1.18	Hippo	0.89	0.71
Parahipp	1.06	1.12	Thalamus	0.85	0.12
Paracent	0.78	0.88	Caud	1.09	0.93
ParsOp	2.38	1.75	Putamen	1.39	1.35
ParsOrb	1.20	1.41	Pallidum	0.22	0.31
ParsTri	0.83	0.72	Amygdala	1.20	1.11
Calcarine	1.09	0.99	Accumbens	1.08	1.16
PostCent	1.33	1.08	InfLatVent	0.99	1.03

Studies of the Gray Matter - Morphometry

Exploratory analyses - not hypothesis driven

- Next step:
  - See if combination of measures can be used in a meaningful way to discriminate between the group
  - Postulate of a network involved
  - Data driven (i.e. all regions with odds ration > 1.5)
  - Further exploration of the pallidum

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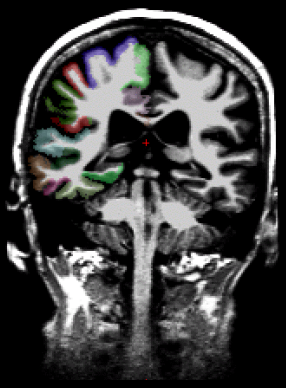
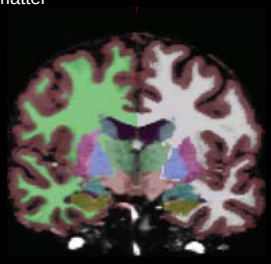
Studies of Gray Matter Summary



- Findings are unclear at this time.
- Profile of differences is not consistent with the findings of others
  - Cingulate gyrus
  - Head of the hippocampus
  - May be due to measurement differences
    - Freesurfer measures of the gray matter do not contain white matter



Studies of Gray Matter Future Analyses

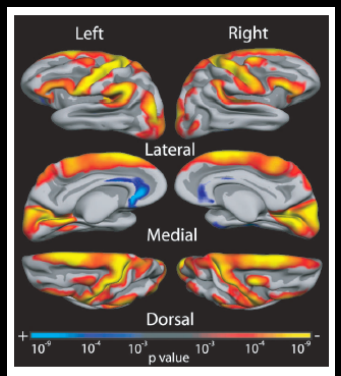


Figure 3. Age-associated map of cortical thinning. Surface maps of cortical thinning in aging were generated by assessing the influence of age on thickness (using the general linear model) at each vertex across the entire cortical mantle. Maps are presented on the semi-inflated cortical surface of an average brain with dark gray regions representing sulci and light gray regions representing gyri. Non-neocortical regions and regions that are not part of the cortical mantle (such as the corpus callosum and thalamus) have been excluded from the analysis. The colorscale at the bottom represents the significance of the thickness change with yellow indicating regions of most significant thinning.

- Complete data-driven analyses to determine optimal set of measures that differentiate the groups.
- Consider more linear analyses such as a general linear model (GLM) looking at cortical thickness and symptom score.

Summary and Recommendation

- Studies continue to suggest CNS differences between subjects with high and low self reported symptoms.
  - Primarily white matter findings
  - Less clear role of the impact on the gray matter
- Consistency is being to emerge in the findings though no clinical marker evident to date
- Nationwide imaging initiative needed
  - Increase study sample sizes
  - Standardize imaging techniques
  - Allow for a wider variety of tools to be applied to this disorder

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Questions?