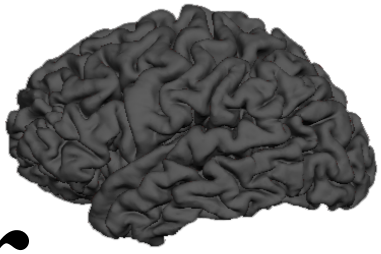

FreeSurfer Tutorial & Workshop

September 26-29, 2016

http://freesurfer.net/fswiki/FsTutorial

Athinoula A. Martinos Center for
Biomedical Imaging
Charlestown, MA 02129

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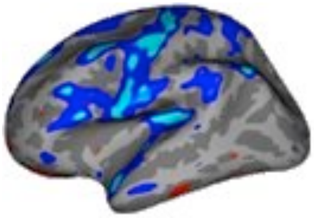

Acknowledgements

The Ellison Medical Foundation

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MIND

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National Center for Research Resources

NIBIB

Monday, September 26th

Time	**Title**	**Type**	**Lecturer**
8:30 - 9:00	** Intro to Linux for FreeSurfer Users	talk/demo	Zeke Kaufman
9:00 - 9:15	** Intro to FreeSurfer Jargon	talk	Allison Stevens & Lilla Zöllei
9:15 - 9:30	**break**		
9:30 - 10:00	Introduction to Freesurfer	talk	Bruce Fischl
10:00 - 11:10	Analyzing the Individual Subject	talk	Doug Greve
11:10 - 11:30	**break**		
11:30 - 11:45	Freeview demonstration	demo	Allison Moreau
11:45 - 12:15	Interaction with Individual Subject Data Tutorial	tutorial	staff
12:15 - 1:15	**Lunch**	--	--
1:15 - 1:45	Interaction with Individual Subject Data Tutorial	tutorial	staff
1:45 - 2:15	Surface-based Analysis: Intersubject Registration & Smoothing	talk	Lilla Zöllei
2:15 - 2:35	**break**		
2:35 - 3:05	ROI Analysis	talk	Doug Greve
3:05 - 3:55	ROI Analysis Tutorial	tutorial	staff
3:55 - 4:25	** A Non-physicist's Intro to MR	talk	Dylan Tisdall
4:25 - 4:55	* MRI Acquisition Methods	talk	André van der Kouwe
4:55 - 5:15	* Motion-compensated Neuroanatomical Imaging	talk	Dylan Tisdall

Tuesday, September 27th

Time	Title	Type	Lecturer
9:00 - 9:50	Group Analysis	talk	Emily Lindemer
9:50 - 10:30	Group Analysis Tutorial	tutorial	staff
10:30 - 10:50	**break**		
10:50 - 11:10	Multiple Comparisons	talk	Doug Greve
11:10 - 11:30	Multiple Comparisons Tutorial	tutorial	staff
11:30 - 11:50	QDEC demonstration	demo	Doug Greve
11:50 - 12:50	**Lunch**	--	--
12:50 - 1:30	QDEC Tutorial	tutorial	staff
1:30 - 2:15	Longitudinal FreeSurfer	talk	Lilla Zöllei
2:15 - 2:55	Longitudinal Tutorial	tutorial	staff
2:55 - 3:15	**break**		
3:15 - 3:45	FreeSurfer Troubleshooting	talk	Bruce Fischl
3:45 - 4:45	Troubleshooting Tutorial	tutorial	staff
4:45 - 5:45	Quality Checking a Recon	demo	Allison Stevens
6:30 - ?	Boston Beer Works	social	staff

Wednesday, September 28th

Time	Title	Type	Lecturer
9:00 - 9:30	Multi-Modal Integration, Part 1	talk	Lilla Zöllei
9:30 - 10:00	Multi-Modal Integration Tutorial	tutorial	staff
10:00 - 10:15	** Intro to Diffusion MRI Physics	talk	Dylan Tisdall
10:15 - 10:35	**break**		
10:35 - 11:15	Introduction to Diffusion MRI	talk	Anastasia Yendiki
11:15 - 12:00	Diffusion Processing Tutorial	tutorial	staff
12:00 - 1:00	**Lunch**	--	--
1:00 - 2:00	TRActs Constrained by UnderLying Anatomy (TRACULA)	talk	Anastasia Yendiki
2:00 - 3:00	Tracula Tutorial	tutorial	staff
3:00 - 3:10	Longitudinal TRACULA	talk	Anastasia Yendiki
3:10 - 3:30	**break**		
3:30 - 4:30	Basics of fMRI Analysis	talk	Jon Polimeni
4:30 - 5:10	FSFAST, Part 1: Preprocessing	talk	Doug Greve

Thursday, September 29th

Time	**Title**	**Type**	**Lecturer**
9:00 - 9:40	FSFAST, Part 2: GLM Analysis	talk	Doug Greve
9:40 - 10:40	FSFAST Tutorial	tutorial	staff
10:40 - 11:00	**break** & Evaluation		
11:00 - 11:30	Multi-Modal Integration, Part 2	talk	Doug Greve
11:30 - 12:00	Multi-Modal Integration Tutorial: fMRI Integration & Surface-based Group fMRI Analysis	tutorial	staff
12:00 - 1:00	**Lunch**	--	--
1:00 - 1:40	* An Overview of Registration Methods	talk	Lilla Zöllei
1:40 - 2:25	Future Directions	talk	Bruce Fischl
2:25 - 2:45	Question & Answer Session	--	staff

FreeSurfer Course, September 26-29 Talk Descriptions

* Indicates an optional technical talk. These talks have great content. They are related to, but not directly about, the FreeSurfer processing stream.
** Indicates an optional talk that covers basic/beginner material.

Day 1: Introduction / Single Subject Analysis / ROI Analysis / MR Acquisition

- ****Intro to Linux for FreeSurfer Users**
  - This linux tutorial is very basic. **Scripting will not be covered.** This tutorial will cover how to to navigate (cd) through directories, how to copy files, how to make directories, how to use emacs, and how to set variables. For those who are not familiar with Linux, this tutorial is meant to get you comfortable enough to at least get through the FreeSurfer tutorials that are part of the course. If you have never used Linux before, this session is highly recommended.
- ****Introduction to FreeSurfer Jargon**
  - Intended for those new to imaging software. Explains basic vocabulary such as voxel, surface, vertex, volume, segmentation, parcellation, registration, and recon.
- **Introduction to FreeSurfer**
  - Overview of FreeSurfer's abilities.
- **Analyzing the Individual Subject in FreeSurfer**
  - Description of each step of the FreeSurfer processing stream.
- **Freeview demonstration**
  - The basics of using Freeview.
- **Interaction with Individual Subject Data - Tutorial**
  - Using FreeSurfer's visualization tools to look at FreeSurfer output.
- **Surface-based Smoothing/Surface-based Registration**
  - Volume vs. Surface-based analysis
- **Region of Interest (ROI) Analysis - Talk and Tutorial**
  - A description of the FreeSurfer atlases used in subcortical segmentation and cortical parcellation as well as the measures FreeSurfer provides. Information on creating and analyzing ROIs (volume vs. intensity studies).
- ****A Non-physicist's Intro to MR**
  - A short introduction to the basic processes underlying MR imaging, with an emphasis on intuitive explanations for non-physicist MR users.
- ***MRI Acquisition Methods for Morphometry**
  - A description of how using different scan protocols can affect data quality and FreeSurfer reconstruction.
- ***Motion-compensated neuroanatomical imaging**
  - While real-time fMRI motion correction has been available with some MRI scanners for years (e.g. Siemens' PACE), effective real-time motion correction in neuroanatomical imaging is just now becoming available. This talk focuses on the motion-correction

system we have developed for the Siemens platform, but also discusses the current developments on the GE platform.

Day 2: Group Analysis / Longitudinal Analysis / Troubleshooting

- **Group Analysis- Talk and Tutorial**
  - Review of linear algebra & other group analysis basics. Covers the basics of group analysis in the context of imaging data.
- **Multiple Comparisons- Talk and Tutorial**
  - How to correct group analysis findings for false discoveries.
- **QDEC (group analysis software) - Demonstration and Tutorial**
  - Introduction to a user-friendly tool for conducting group analyses.
- **Longitudinal FreeSurfer - Talk and Tutorial**
  - How to process longitudinal data with FreeSurfer and what's going on behind the scenes.
- **FreeSurfer Troubleshooting - Talk and Tutorial**
  - Discussion of the possible errors one may find in their FreeSurfer output and how to fix them.
- **Quality Checking a Recon - Demonstration**
  - Live demo of how to scroll through FreeSurfer output and look for errors.

Day 3: Multimodal Analysis / Diffusion Analysis / fMRI Analysis

- **Multi-Modal Integration, Part 1: Registration – Talk and Tutorial**
  - Introduction on how FreeSurfer output can be used with other modalities (i.e. fMRI data, diffusion data). How to register surface data with other modalities using FreeSurfer.
- ****A Non-physicist's Intro to Diffuision MR**
  - A short introduction to the basic processes underlying Diffusion MR imaging, with an emphasis on intuitive explanations for non-physicist MR users.
- **Introduction to Diffusion MRI, Diffusion Data Processing – Talk and Tutorial**
  - How to process diffusion MRI data to extract basic diffusion measures.
- **TRActs Constrained by UnderLying Anatomy (TRACULA), Longitudinal TRACULA – Talks and Tutorial**
  - How to reconstruct white-matter pathways using FreeSurfer's*new* tractography tool.
- **Basics of fMRI Analysis**
  - Covers the basics of functional MRI data analysis, spanning preprocessing to single-subject and group-level analyses. Topics include motion correction, B0 distortion correction, spatial normalization, spatial smoothing, hemodynamic modeling, GLM analysis, contrasts and hypothesis testing, and Random-, Fixed-, and Mixed-Effects group analyses.
- **FSFAST, Part 1: Preprocessing**

    - Preprocessing of fMRI (motion correction, slice-timing correction, smoothing, registration to the anatomical, sampling to the common group space in the surface and volume), setting up and running block and event-related analysis, and adding nuisance variables to the analysis.

Day 4: fMRI Analysis / Multimodal Analysis / Future Directions

- **FSFAST, Part 2: GLM Analysis – Talk and Tutorial**
    - Performing the individual fMRI time series fMRI analysis and performing group fMRI analysis in the volume and on the surface.
- **Multi-Modal Integration, Part 2 - Talk and Tutorial**
    - Introduction on how FreeSurfer output can be used with other modalities (i.e. fMRI data, diffusion data). How to integrate fMRI with other modalities, and how to run surface-based group fMRI analysis.
- ***An Overview of Registration Methods**
    - Overview of different registration methods discussed so far (flirt, robust_register, bbregister) and introduction of a new registration tool, CVS (combined volume and surface registration).
- **Future Directions of FreeSurfer**
    - A look at some of the current research and features the FreeSurfer Development team has been working on.
- **Question and Answer Session**
    - Open forum to resolve any unanswered questions

FreeSurfer System Requirements

Summary of Requirements:
Operating System: Linux, Mac OS X, Windows (via VirtualBox)
Processor Speed: 2GHz at least
RAM: 8GB recommended
Graphics card: 3D graphics card with its own graphics memory & accelerated OpenGL drivers
Size of installation package: 14GB
Typical size of a processed subject: 370MB
Tutorial dataset size: 5Gigs
Other requirements: Matlab (only needed to run FS-FAST, the fMRI analysis stream)

Freesurfer is available for the Linux and Mac OS X operating systems. It can also be used on Windows with VirtualBox (but runs a bit slower). The download page lists the supported platforms. Matlab is required to run the FS-FAST component of Freesurfer (but Matlab is not required to run the reconstruction utilities).

A 2GHz or faster processor, at least 4GB of RAM, and a 3D graphics card (with its own graphics memory) with accelerated OpenGL drivers, is recommended. Freesurfer is highly CPU and memory intensive (and moderately disk intensive), so concentrate on boosting those performance aspects (more memory is better...**8GB is highly recommended!**).

With the inclusion of new OpenMP-enabled code in freesurfer, multiple-cores can now be accessed by recon-all. This means you should also consider purchasing a multi-core machine if you intend to process multiple subjects at the same time. If you do this, be sure to purchase 4GB per subject, that is, if you would like to process four subjects at once, your machine must have four cores and 16GB of memory. The flag you would include with recon-all to do this is: `-openmp 4` which tells recon-all to use four cores (cpus) when the special parallelized code is run (ie. the 'gcareg' stage).

Most modern video graphics card will perform fine, but be aware that graphics cards that use CPU memory as video memory will have a noticeably slow redraw rate. NVidia graphics cards have been found to work best with freesurfer. While freesurfer includes some GPU support, it is not actively supported anymore, so purchasing a GPU card explicitly for freesurfer is not recommended, in lieu of purchasing multiple cores and using the OpenMP functionality (-openmp <num_threads> flag). A 19" (or greater!) monitor is also recommended.

If you're running Freesurfer on a server, then allocate 4GB of memory to your job.

Freesurfer requires about 8.5GB of disk space for the full installation, which includes the Freesurfer binaries, support libraries, the MINC toolkit, and sample MRI data.

The volume and surface data files produced by Freesurfer for a typical subject (assuming two structural MRI scans of source data) consume about 370MB of disk space. The full tutorial dataset is 18GB.

Mailing list notes regarding **suggested specs for a Linux box**:

- CPU: Intel vs AMD: no preference. also, CPU speed is not critical. It is better to have at least 4GB, and budget 4GB per subject you want to process simultaneously. Try to get an 'Ivy Bridge' motherboard architecture or whatever is newer. This allows better addressing of scattered memory which is common in freesurfer, and it alone accounts for a 5% or so speedup. AMD might have a similar memory controller.
- Graphics card:
  - ATI (AMD) vs nVidia: We still spec nVidia because we don't have problems with its OpenGL-X driver under linux. Perhaps ATI has finally supplied one that works, but this hasn't been attempted in a couple years. ATI cards on the Mac work fine with freesurfer though.
  - GPU: We no longer support [further] CUDA or GPU development because of lack of resources and difficulty, in preference to using OpenMP, which uses CPU cores. We will continue to support the existing GPU CUDA code that runs on recon-all with the -use-gpu switch. By support, keeping it running with each new nvidia cuda driver release as best as we can.
- Disk: Freesurfer is not disk intensive, so SSD is not a benefit. Budget 400MB per subject for storage.
- Linux: Both freesurfer and fsl groups use CentOS 6 in our Centers. It seems to work well.

SystemRequirements (last edited 2016-04-21 14:06:27 by ZekeKaufman)

Processing in FreeSurfer: An example pipeline from start to finish

INDIVIDUAL SUBJECT:

```
 >>  recon-all -all -s <>
   >  Edit output
 >>  recon-all -make all -s <>
```

LONGITUDINAL:

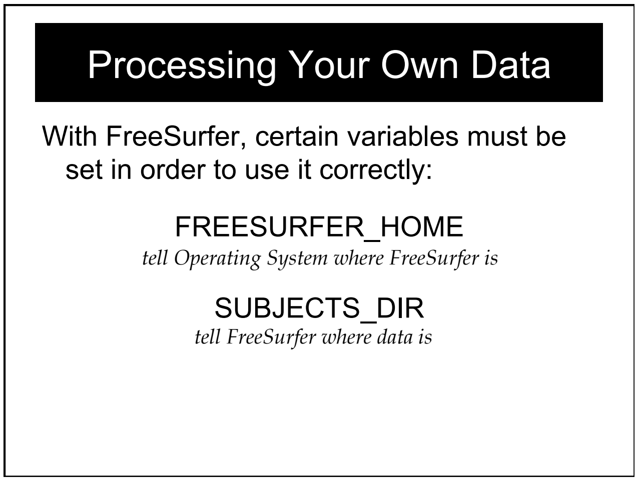
```
 >>  recon-all -base <> -tp <> -all
 >>  recon-all -long <> -tp <> -all
```

1ST LEVEL ANALYSIS:

```
 >>  recon-all -s <> -qcache
   >  Create FSGD and contrast files
 >>  mris_preproc --fsgd <> --cache-in <> --target fsaverage --hemi <> --out <> --fwhm <>
 >>  mri_glmfit --y <> --fsgd <> --C <> --surf fsaverage <> --cortex --glmdir <>
 >>  mri_glmfit-sim --glmdir <> --cache <> <> --cwp <> --2spaces
```

MULTIMODAL INTEGRATION:

```
 >>  bbregister --mov <> --s <>  --lta <>
 >>  mri_vol2vol or mri_vol2surf
 >>  mris_preproc --iv <> <> --iv <> <>
 >>  mri_glmfit --y <> --fsgd <> --C <> --surf fsaverage <> --cortex --glmdir <>
 >>  mri_glmfit-sim --glmdir <> --cache <> <> --cwp <> --2spaces
```

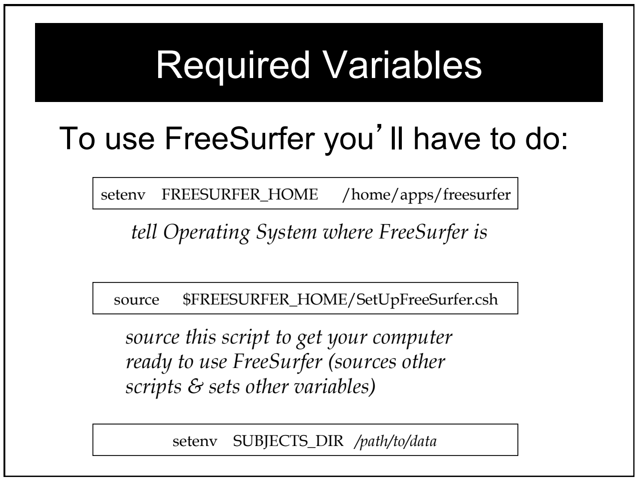


Processing Your Own Data

With FreeSurfer, certain variables must be set in order to use it correctly:

FREESURFER_HOME
tell Operating System where FreeSurfer is

SUBJECTS_DIR
tell FreeSurfer where data is



Required Variables

To use FreeSurfer you'll have to do:

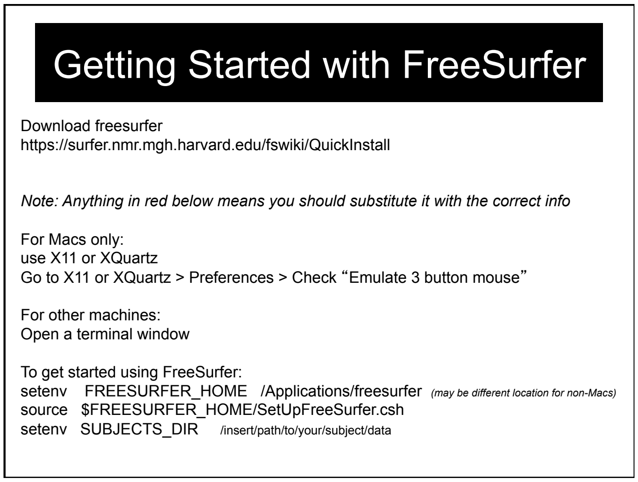
```
setenv   FREESURFER_HOME     /home/apps/freesurfer
```

tell Operating System where FreeSurfer is

```
source     $FREESURFER_HOME/SetUpFreeSurfer.csh
```

source this script to get your computer ready to use FreeSurfer (sources other scripts & sets other variables)

```
setenv   SUBJECTS_DIR  /path/to/data
```



Getting Started with FreeSurfer

Download freesurfer
https://surfer.nmr.mgh.harvard.edu/fswiki/QuickInstall

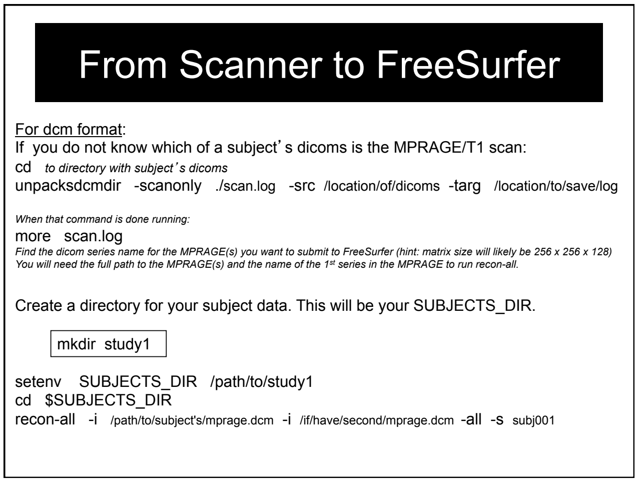
Note: Anything in red below means you should substitute it with the correct info

For Macs only:
use X11 or XQuartz
Go to X11 or XQuartz > Preferences > Check "Emulate 3 button mouse"

For other machines:
Open a terminal window

To get started using FreeSurfer:

```
setenv    FREESURFER_HOME    /Applications/freesurfer  (may be different location for non-Macs)
source   $FREESURFER_HOME/SetUpFreeSurfer.csh
setenv   SUBJECTS_DIR     /insert/path/to/your/subject/data
```



From Scanner to FreeSurfer

For dcm format:
If you do not know which of a subject's dicoms is the MPRAGE/T1 scan:

```
cd   to directory with subject's dicoms
unpacksdcmdir   -scanonly   ./scan.log   -src  /location/of/dicoms  -targ   /location/to/save/log
```

When that command is done running:

```
more   scan.log
```

Find the dicom series name for the MPRAGE(s) you want to submit to FreeSurfer (hint: matrix size will likely be 256 x 256 x 128)
You will need the full path to the MPRAGE(s) and the name of the 1st series in the MPRAGE to run recon-all.

Create a directory for your subject data. This will be your SUBJECTS_DIR.

```
mkdir  study1
```

```
setenv    SUBJECTS_DIR   /path/to/study1
cd   $SUBJECTS_DIR
recon-all   -i   /path/to/subject's/mprage.dcm  -i  /if/have/second/mprage.dcm  -all  -s  subj001
```

GLOSSARY

anatomically derived defect

- A topological defect in the cortical surface that arises from a feature of normal neuroanatomy to be distinguished from defects arising entirely from segmentation errors. See topological defect

artifact

- A feature that appears in an image but is not actually present in the imaged object.

average convexity

- The signed distance that a vertex moves during the inflation process.

brain volume

- The T1 volume after the skull and other non-brain structures have been removed. This volume can be viewed using tkmedit.

canonical surface

- Surface-based atlas constructed from the cortical surfaces of 40 normal individuals (used for inter-subject averaging).

conversion/averaging

- Process of converting and averaging multiple structural acquisitions from the native magnet format into the native FreeSurfer format (see COR files).

COR files

- The native file format used by FreeSrurfer to store 3D structural image data.

Euler number

- After Leonhard Euler (1707-83). A topological invariant of a surface that can be computed from the number of edges, vertices and faces in a polygonal tessellation (command mris_euler_number). The Euler number of a sphere will equal 2; the Euler number of a surface with n handles is 2 - 2n.

filled volume

- The wm volume after separation of the left and right hemispheres and filling of each hemisphere. This volume can be viewed using tkmedit.

flattening

- Producing a planar (flat) representation of a patch of the cortical surface that has minimal metric distortion.

gyrus

- A fold or convolution of brain tissue (an outward folded region).

inflated surface

- The smoothwm surface after inflation. This surface can be viewed using surfer.

inflation

- The process of smoothing the cortex while minimizing metric distortion, so that all sulci are fully visible and surface distances are apparent to visual inspection.

intensity

- Measured amount of magnetic field at a given spatial location, represented by a voxel (higher SNR signal to noise ratio means voxels will have a higher intensity relative to the background noise, and appear brighter).

label

- A particular region of interest. e.g. in tksurfer the label would be a region of interest in the surface. In tkmedit a label is a region of interest in the volume.

morphing

- Computer graphics technique whereby a mapping is computed that smoothly transforms one image or surface into another.

morphometrics

- The study of geometric properties of the human brain.

motion correction

- Processing multiple structural volumes so that the effects of subject movement are minimized. This is typically done by aligning multiple images/volume to an initial image/volume (see conversion/averaging).

MRI volume

- The three dimensional volumetric data set collected from a MRI scanner.

orig volume

- The original MRI volume. This volume can be viewed using tkmedit.

orig surface

- The first surface constructed by covering the labeled voxels in the filled volume. This surface can be viewed using surfer.

pial

- Pertaining to the delicate pia mater which envelops the brain (gray matter). Also, the model of the pial surface (?h.pial).

pial surface

- The refined estimate of the gray/CSF boundary (pial surface). This surface can be viewed using surfer.

region growing process

- An algorithm that groups voxels or sub-regions into larger regions.

RF-field inhomogeneities

- Spatial variations in the Radio Frequency (RF) excitation pulse. These variations result in changes in the measured intensity for a given tissue class that are related to the spatial location of the voxel.

segmentation

- Labeling of tissue classes from MRI data (e.g. white matter).

smoothing

- Process of producing a relatively even and regular cortical surface.

smoothwm surface

- The orig surface after smoothing. This surface can be viewed using surfer.

sulcus

- A groove or furrow in brain tissue (an inward folded region).

supertessellated icosahedron

- Polygonal approximation to a sphere.

T1

- Longitudinal relaxation constant.

T1 volume

- The MRI volume after intensity normalization. This volume can be viewed using tkmedit.

T1 Weighted Image

- A magnetic resonance image where the contrast is predominantly dependent on T1.

T2 Weighted Image

- A magnetic resonance image where the contrast is predominantly dependent on T2.

T2

- Transverse relaxation constant.

Talairach coordinate

- The corresponding location in the Talairach atlas for a given point in a brain that has been coregistered with the atlas (Talairach et al, 1967).

tessellation

- Covering of a surface by repeated use of a single shape.

topology

- The properties of a surface related to its connectivity that are unaffected by geometric (i.e. rubber sheet) transformations.

topological defect

- A portion of a surface that results in the surface topology differing from that of a sphere.

volume

- A 3-D data set that typically contains either intensity information derived from the original MRI, or the results of segmenting this data into tissue classes.

voxel

- The basic element of an MRI volume (analogous to a pixel in a 2-D image). The volume of a structural voxel is approximately 1 mm^3.

white surface

- The refined estimate of the gray/white boundary. This surface can be viewed using surfer.

wm volume

- The brain volume after white matter segmentation. This is also the volume that is manually edited. This volume can be viewed using tkmedit.

What is Linux?

- Most common household computer
- 90% of all internet traffic comes from Windows based machines*
- Especially popular in the gaming community

- 9% of all internet traffic comes from OSX based machines
- Especially popular in the photo, video, and music editing communities

- Open source operating system
- 1% of all internet traffic comes from Linux based machines
- Widely used in academia, supercomputers, and web servers

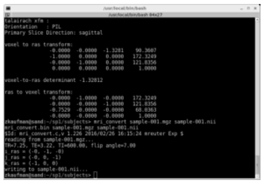
---

* https://en.wikipedia.org/wiki/Usage_share_of_operating_systems

Linux Desktop

```
ubuntu@ubuntu-VirtualBox:~>  ls -l
total 44
drwxr-xr-x 2 ubuntu ubuntu 4096 Oct 23  2012 Desktop
drwxr-xr-x 2 ubuntu ubuntu 4096 Oct 23  2012 Documents
drwxr-xr-x 2 ubuntu ubuntu 4096 Oct 23  2012 Downloads
-rw-r--r-- 1 ubuntu ubuntu 8445 Oct 23  2012 examples.desktop
drwxr-xr-x 2 ubuntu ubuntu 4096 Oct 23  2012 Music
drwxr-xr-x 2 ubuntu ubuntu 4096 Oct 23  2012 Pictures
drwxr-xr-x 2 ubuntu ubuntu 4096 Oct 23  2012 Public
drwxr-xr-x 2 ubuntu ubuntu 4096 Oct 23  2012 Templates
drwxr-xr-x 2 ubuntu ubuntu 4096 Oct 23  2012 Videos
ubuntu@ubuntu-VirtualBox:~>  ping sand
PING sand.nmr.mgh.harvard.edu (172.20.82.51) 56(84) bytes of data.
64 bytes from sand.nmr.mgh.harvard.edu (172.20.82.51): icmp_req=1 ttl=63 time=0.40
3 ms
64 bytes from sand.nmr.mgh.harvard.edu (172.20.82.51): icmp_req=2 ttl=63 time=0.68
1 ms
64 bytes from sand.nmr.mgh.harvard.edu (172.20.82.51): icmp_req=3 ttl=63 time=0.64
7 ms
^C
--- sand.nmr.mgh.harvard.edu ping statistics ---
3 packets transmitted, 3 received, 0% packet loss, time 2002ms
rtt min/avg/max/mdev = 0.403/0.577/0.681/0.123 ms
ubuntu@ubuntu-VirtualBox:~>
```

Terminal does not mean "hacking"

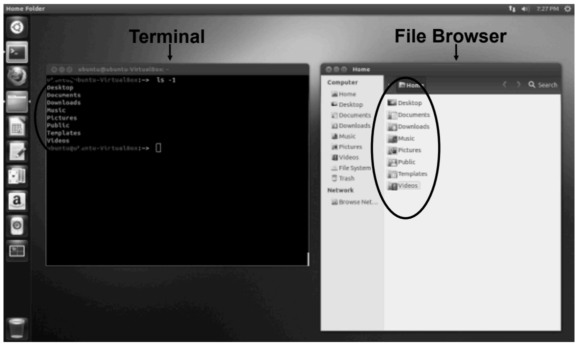


```
talairach xfm :
Orientation   : PIL
Primary Slice Direction: sagittal

voxel to ras transform:
              -0.0000  -0.0000  -1.3281    90.3607
              -1.0000   0.0000   0.0000   172.3249
              -0.0000  -1.0000   0.0000   121.8356
               0.0000   0.0000   0.0000     1.0000

voxel-to-ras determinant -1.32812

ras to voxel transform:
              -0.0000  -1.0000  -0.0000   172.3249
              -0.0000  -0.0000  -1.0000   121.8356
              -0.7529  -0.0000  -0.0000    68.0363
              -0.0000  -0.0000  -0.0000     1.0000
zkaufman@sand:~/spl/subjects> mri_convert sample-001.mgz sample-001.nii
mri_convert.bin sample-001.mgz sample-001.nii
$Id: mri_convert.c,v 1.226 2016/02/26 16:15:24 mreuter Exp $
reading from sample-001.mgz...
TR=7.25, TE=3.22, TI=600.00, flip angle=7.00
i_ras = (-0, -1, -0)
j_ras = (-0, 0, -1)
k_ras = (-1, 0, 0)
writing to sample-001.nii...
zkaufman@sand:~/spl/subjects>
```

≠

Tank: The "operator" of the Nebuchadnezzar, a "natural" human born outside of the Matrix

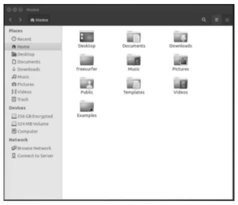
Terminal gives you access to your computer via typing commands rather than using the mouse and clicking

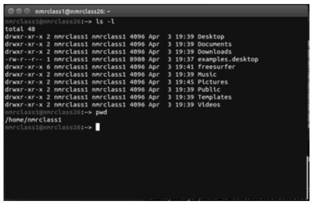


```
ubuntu@ubuntu-VirtualBox:~>  ls -1
Desktop
Documents
Downloads
Music
Pictures
Public
Templates
Videos
ubuntu@ubuntu-VirtualBox:~>
```

Demonstration of commands

Task: *Navigate to the freesurfer directory, list its content, then create a new directory called Practice and create a simple text file called Notes.txt.*





```
nmrclass1@nmrclass26:~> ls -l
total 48
drwxr-xr-x 2 nmrclass1 nmrclass1 4096 Apr  3 19:39 Desktop
drwxr-xr-x 2 nmrclass1 nmrclass1 4096 Apr  3 19:39 Documents
drwxr-xr-x 2 nmrclass1 nmrclass1 4096 Apr  3 19:39 Downloads
-rw-r--r-- 1 nmrclass1 nmrclass1 8980 Apr  3 19:37 examples.desktop
drwxr-xr-x 6 nmrclass1 nmrclass1 4096 Apr  3 19:41 freesurfer
drwxr-xr-x 2 nmrclass1 nmrclass1 4096 Apr  3 19:39 Music
drwxr-xr-x 2 nmrclass1 nmrclass1 4096 Apr  3 19:45 Pictures
drwxr-xr-x 2 nmrclass1 nmrclass1 4096 Apr  3 19:39 Public
drwxr-xr-x 2 nmrclass1 nmrclass1 4096 Apr  3 19:39 Templates
drwxr-xr-x 2 nmrclass1 nmrclass1 4096 Apr  3 19:39 Videos
nmrclass1@nmrclass26:~> pwd
/home/nmrclass1
nmrclass1@nmrclass26:~>
```

Demo

Using Freesurfer

- **Up to this point, we have not done anything freesurfer related**
- **Once Freesurfer is installed, many more commands become available to you**
- **With Freesurfer, certain variables must be set in order to use it correctly**

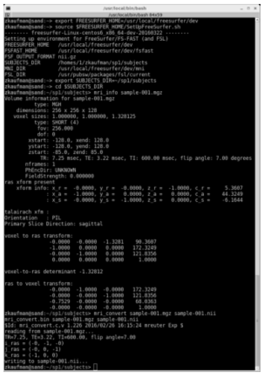
`FREESURER_HOME`	Tells operating system where freesurfer is installed
`SUBJECTS_DIR`	Tells Freesurfer where your subject data is

Exercise: *Use Freesurfer to display header information of an mri image file, then convert it to nifti format, then display the resulting image in the freeview application.*

Exercise

Use Freesurfer to display header information of an mri image file, and convert it to nifti:

```
$> export FREESURFER_HOME=/home/nmrclass/freesurfer
$> source $FREESURFER_HOME/SetUpFreeSurfer.sh
$> export SUBJECTS_DIR=$FREESURFER_HOME/subjects
$> cd $SUBJECTS_DIR
$> mri_info sample-001.mgz
…
$> mri_convert sample-001.mgz sample-001.nii
…
$> freeview sample-001.nii
```



```
zkaufman@sand:~> export FREESURFER_HOME=/usr/local/freesurfer/dev
zkaufman@sand:~> source $FREESURFER_HOME/SetUpFreeSurfer.sh
-------- freesurfer-Linux-centos6_x86_64-dev-20160322 --------
Setting up environment for FreeSurfer/FS-FAST (and FSL)
FREESURFER_HOME   /usr/local/freesurfer/dev
FSFAST_HOME       /usr/local/freesurfer/dev/fsfast
FSF_OUTPUT_FORMAT nii.gz
SUBJECTS_DIR      /homes/1/zkaufman/spl/subjects
MNI_DIR           /usr/local/freesurfer/dev/mni
FSL_DIR           /usr/pubsw/packages/fsl/current
zkaufman@sand:~> export SUBJECTS_DIR=~/spl/subjects
zkaufman@sand:~> cd $SUBJECTS_DIR
zkaufman@sand:~/spl/subjects> mri_info sample-001.mgz
Volume information for sample-001.mgz
          type: MGH
    dimensions: 256 x 256 x 128
   voxel sizes: 1.000000, 1.000000, 1.328125
          type: SHORT (4)
           fov: 256.000
           dof: 0
        xstart: -128.0, xend: 128.0
        ystart: -128.0, yend: 128.0
        zstart: -85.0, zend: 85.0
            TR: 7.25 msec, TE: 3.22 msec, TI: 600.00 msec, flip angle: 7.00 degrees
       nframes: 1
       PhEncDir: UNKNOWN
       FieldStrength: 0.000000
ras xform present
    xform info: x_r =  -0.0000, y_r =  -0.0000, z_r =  -1.0000, c_r =     5.3607
              : x_a =  -1.0000, y_a =   0.0000, z_a =   0.0000, c_a =    44.3249
              : x_s =  -0.0000, y_s =  -1.0000, z_s =   0.0000, c_s =    -6.1644

talairach xfm :
Orientation   : PIL
Primary Slice Direction: sagittal

voxel to ras transform:
               -0.0000  -0.0000  -1.3281    90.3607
               -1.0000   0.0000   0.0000   172.3249
               -0.0000  -1.0000   0.0000   121.8356
                0.0000   0.0000   0.0000     1.0000

voxel-to-ras determinant -1.32812

ras to voxel transform:
               -0.0000  -1.0000  -0.0000   172.3249
               -0.0000  -0.0000  -1.0000   121.8356
               -0.7529  -0.0000  -0.0000    68.0363
               -0.0000  -0.0000  -0.0000     1.0000
zkaufman@sand:~/spl/subjects> mri_convert sample-001.mgz sample-001.nii
mri_convert.bin sample-001.mgz sample-001.nii
$Id: mri_convert.c,v 1.226 2016/02/26 16:15:24 mreuter Exp $
reading from sample-001.mgz...
TR=7.25, TE=3.22, TI=600.00, flip angle=7.00
i_ras = (-0, -1, -0)
j_ras = (-0, 0, -1)
k_ras = (-1, 0, 0)
writing to sample-001.nii...
zkaufman@sand:~/spl/subjects> 
```

Demo

More Help

$> mri_info --help
USAGE: mri_info fname1 <fname2> <options>

$> man pwd
NAME
    pwd - print name of current/working directory

UNIX Tutorial For Beginners:
http://www.ee.surrey.ac.uk/Teaching/Unix/

Linux in a Nutshell:
http://docstore.mik.ua/orelly/linux/lnut/ch01_01.htm

UNIX Cheat Sheet:
http://tux.cs.unlv.edu/refs/linux_commands.html

Command Line Tutorial:
http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/CommandLineNavigation

Unix/Linux Command Reference

FOSSwire.com

File Commands

ls – directory listing

ls -al – formatted listing with hidden files

cd *dir* - change directory to *dir*

cd – change to home

pwd – show current directory

mkdir *dir* – create a directory *dir*

rm *file* – delete *file*

rm -r *dir* – delete directory *dir*

rm -f *file* – force remove *file*

rm -rf *dir* – force remove directory *dir* *

cp *file1 file2* – copy *file1* to *file2*

cp -r *dir1 dir2* – copy *dir1* to *dir2*; create *dir2* if it doesn't exist

mv *file1 file2* – rename or move *file1* to *file2* if *file2* is an existing directory, moves *file1* into directory *file2*

ln -s *file link* – create symbolic link *link* to *file*

touch *file* – create or update *file*

cat > *file* – places standard input into *file*

more *file* – output the contents of *file*

head *file* – output the first 10 lines of *file*

tail *file* – output the last 10 lines of *file*

tail -f *file* – output the contents of *file* as it grows, starting with the last 10 lines

Process Management

ps – display your currently active processes

top – display all running processes

kill *pid* – kill process id *pid*

killall *proc* – kill all processes named *proc* *

bg – lists stopped or background jobs; resume a stopped job in the background

fg – brings the most recent job to foreground

fg *n* – brings job *n* to the foreground

File Permissions

chmod *octal file* – change the permissions of *file* to *octal*, which can be found separately for user, group, and world by adding:

- 4 – read (r)
- 2 – write (w)
- 1 – execute (x)

Examples:

chmod 777 – read, write, execute for all

chmod 755 – rwx for owner, rx for group and world

For more options, see **man chmod**.

SSH

ssh *user@host* – connect to *host* as *user*

ssh -p *port user@host* – connect to *host* on port *port* as *user*

ssh-copy-id *user@host* – add your key to *host* for *user* to enable a keyed or passwordless login

Searching

grep *pattern files* – search for *pattern* in *files*

grep -r *pattern dir* – search recursively for *pattern* in *dir*

command* | grep *pattern – search for *pattern* in the output of *command*

locate *file* – find all instances of *file*

System Info

date – show the current date and time

cal – show this month's calendar

uptime – show current uptime

w – display who is online

whoami – who you are logged in as

finger *user* – display information about *user*

uname -a – show kernel information

cat /proc/cpuinfo – cpu information

cat /proc/meminfo – memory information

man *command* – show the manual for *command*

df – show disk usage

du – show directory space usage

free – show memory and swap usage

whereis *app* – show possible locations of *app*

which *app* – show which *app* will be run by default

Compression

tar cf *file.tar files* – create a tar named *file.tar* containing *files*

tar xf *file.tar* – extract the files from *file.tar*

tar czf *file.tar.gz files* – create a tar with Gzip compression

tar xzf *file.tar.gz* – extract a tar using Gzip

tar cjf *file.tar.bz2* – create a tar with Bzip2 compression

tar xjf *file.tar.bz2* – extract a tar using Bzip2

gzip *file* – compresses *file* and renames it to *file.gz*

gzip -d *file.gz* – decompresses *file.gz* back to *file*

Network

ping *host* – ping *host* and output results

whois *domain* – get whois information for *domain*

dig *domain* – get DNS information for *domain*

dig -x *host* – reverse lookup *host*

wget *file* – download *file*

wget -c *file* – continue a stopped download

Installation

Install from source:

```
./configure
make
make install
```

dpkg -i *pkg.deb* – install a package (Debian)

rpm -Uvh *pkg.rpm* – install a package (RPM)

Shortcuts

Ctrl+C – halts the current command

Ctrl+Z – stops the current command, resume with **fg** in the foreground or **bg** in the background

Ctrl+D – log out of current session, similar to **exit**

Ctrl+W – erases one word in the current line

Ctrl+U – erases the whole line

Ctrl+R – type to bring up a recent command

!! - repeats the last command

exit – log out of current session

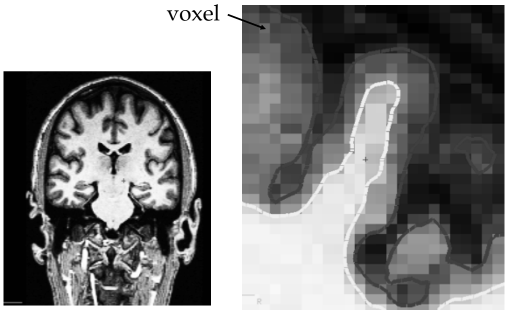
* use with extreme caution.

Intro to FreeSurfer Jargon

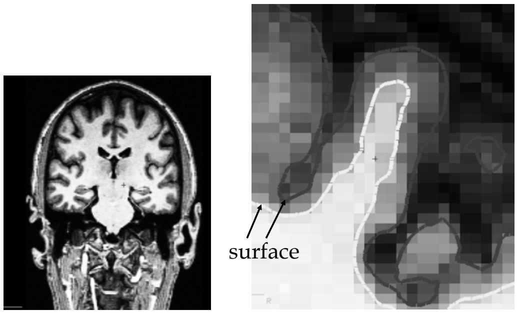
Intro to FreeSurfer Jargon

voxel
surface
volume
vertex
surface-based
recon
cortical, subcortical
parcellation/segmentation
registration, morph, deform, transforms
(computing vs. resampling)

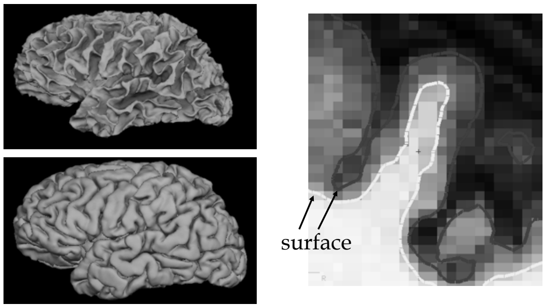
Intro to FreeSurfer Jargon



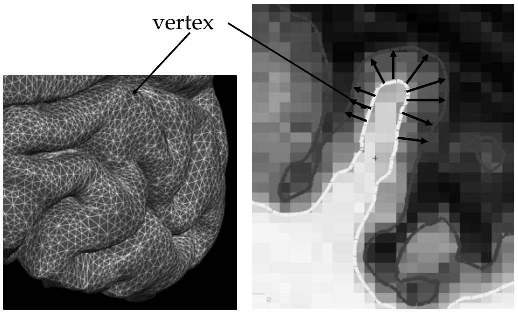
Intro to FreeSurfer Jargon



Intro to FreeSurfer Jargon

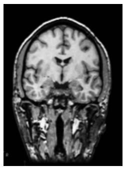


Intro to FreeSurfer Jargon

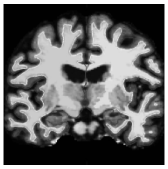


What FreeSurfer Does…

FreeSurfer creates computerized models of the brain from MRI data.



Input:
T1-weighted (MPRAGE)
1mm^3 resolution
(.dcm)

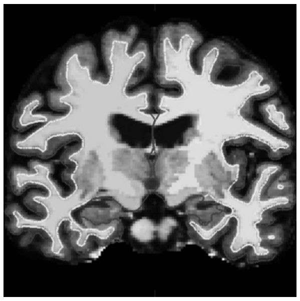


Output:
Segmented & parcellated conformed volume
(.mgz)

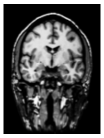
Recon

"*recon* your data"
…short for *reconstruction*
…cortical surface *reconstruction*
…shows up in command *recon-all*

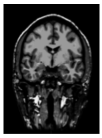
Recon



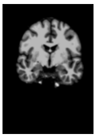
Volumes



orig.mgz



T1.mgz



brainmask.mgz

wm.mgz

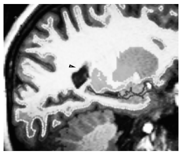
filled.mgz
(Subcortical Mass)

Cortical vs. Subcortical GM

cortical gm

subcortical gm

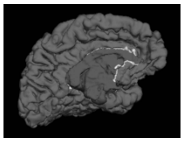
coronal



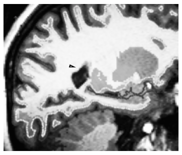
sagittal

Cortical vs. Subcortical GM

subcortical gm



coronal

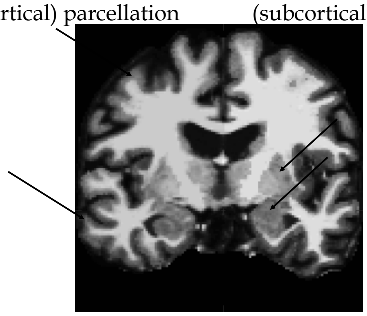


sagittal

Parcellation vs. Segmentation

(cortical) parcellation

(subcortical) segmentation



Intro to FreeSurfer Jargon

voxel
surface
volume
vertex
surface-based
recon
cortical, subcortical
parcellation/segmentation
registration, morph, deform, transforms
(computing vs. resampling)

Registration

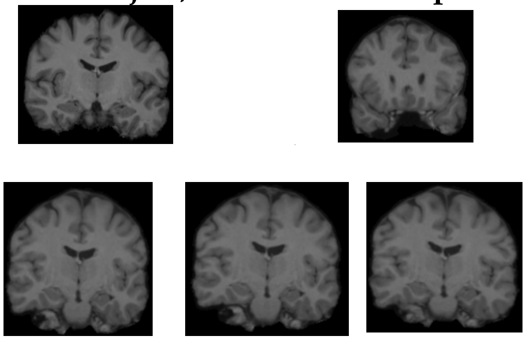
Goal:

to find a common coordinate system for the input data sets

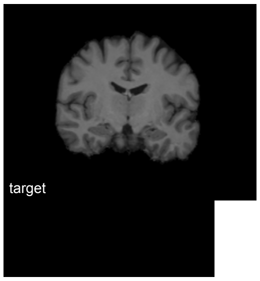
Examples:

- comparing different MRI images of the same individual (longitudinal scans, diffusion vs functional scans)
- comparing MRI images of different individuals

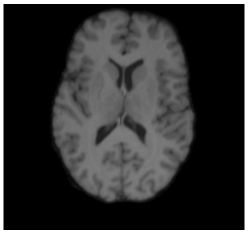
Inter-subject, uni-modal example



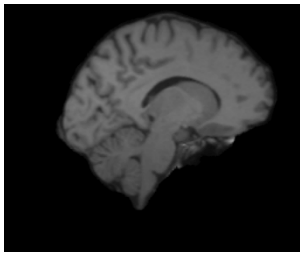
Linear registration: 6, 9, 12 DOF



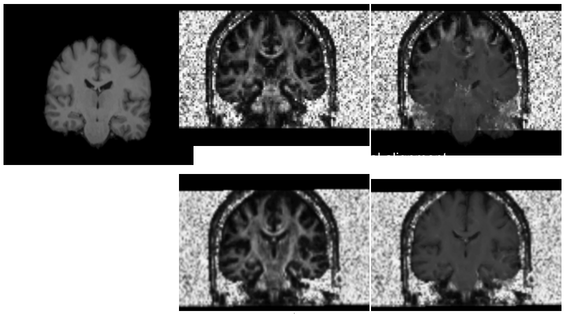
Linear registration: 6, 9, 12 DOF

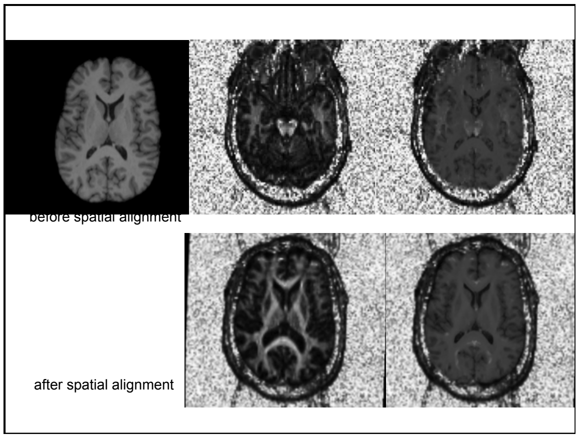


Linear registration: 6, 9, 12 DOF



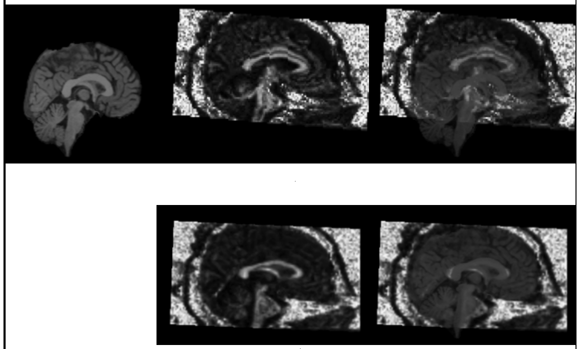
Intra-subject, multi-modal example



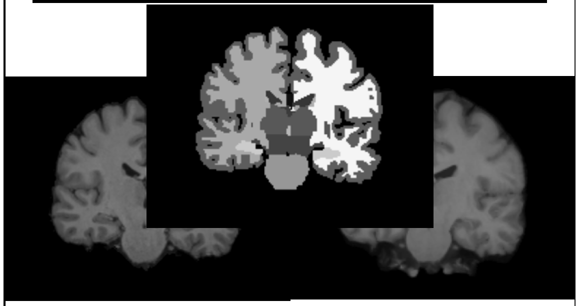


before spatial alignment

after spatial alignment



Inter-subject non-linear example



Some registration vocabulary

- Input datasets:
  - Fixed / template / target
  - Moving / subject
- Transformation models
  - rigid
  - affine
  - nonlinear
- Objective / similarity functions

- Applying the results
  - deform, morph, resample, transform
- Interpolation types
  - (tri)linear
  - nearest neighbor

FreeSurfer Questions

Search for terms and answers
to all your questions in the Glossary, FAQ,
or
FreeSurfer Mailing List Archives

FreeSurfer Introduction

MASSACHUSETTS
GENERAL HOSPITAL

Course Overview

Day 1
- Individual Subject Analysis
- ROI Analysis
- MR Basics & Acquisition Tips

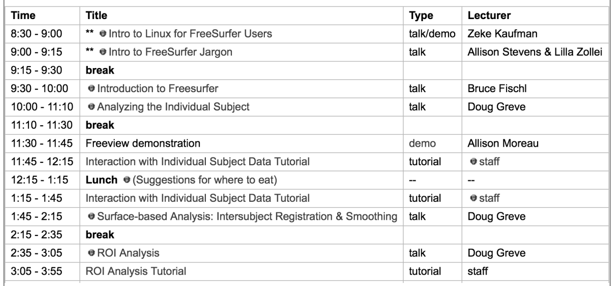
Day 2
- Group Analysis
- Longitudinal Analysis
- Troubleshooting

Day 3
- Multimodal Analysis
- Diffusion Analysis
- fMRI Analysis

Day 4
- fMRI Analysis
- Multimodal Analysis
- Future Directions

Course Schedule

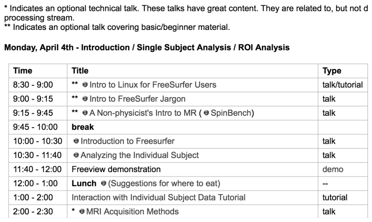
https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/Sept2016CourseSchedule



Time	Title	Type	Lecturer
8:30 - 9:00	** Intro to Linux for FreeSurfer Users	talk/demo	Zeke Kaufman
9:00 - 9:15	** Intro to FreeSurfer Jargon	talk	Allison Stevens & Lilla Zollei
9:15 - 9:30	**break**		
9:30 - 10:00	Introduction to Freesurfer	talk	Bruce Fischl
10:00 - 11:10	Analyzing the Individual Subject	talk	Doug Greve
11:10 - 11:30	**break**		
11:30 - 11:45	Freeview demonstration	demo	Allison Moreau
11:45 - 12:15	Interaction with Individual Subject Data Tutorial	tutorial	staff
12:15 - 1:15	**Lunch** (Suggestions for where to eat)	--	--
1:15 - 1:45	Interaction with Individual Subject Data Tutorial	tutorial	staff
1:45 - 2:15	Surface-based Analysis: Intersubject Registration & Smoothing	talk	Doug Greve
2:15 - 2:35	**break**		
2:35 - 3:05	ROI Analysis	talk	Doug Greve
3:05 - 3:55	ROI Analysis Tutorial	tutorial	staff

Lectures and Practicals

- General format: talk followed by tutorial (both are on the wiki course page, but please don't download tutorial data or FreeSurfer– it can kill the network)



* Indicates an optional technical talk. These talks have great content. They are related to, but not d
processing stream.
** Indicates an optional talk covering basic/beginner material.

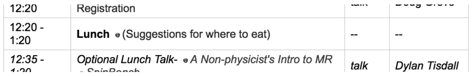
Monday, April 4th - Introduction / Single Subject Analysis / ROI Analysis

Time	Title	Type
8:30 - 9:00	** Intro to Linux for FreeSurfer Users	talk/tutorial
9:00 - 9:15	** Intro to FreeSurfer Jargon	talk
9:15 - 9:45	** A Non-physicist's Intro to MR (SpinBench)	talk
9:45 - 10:00	**break**	
10:00 - 10:30	Introduction to Freesurfer	talk
10:30 - 11:40	Analyzing the Individual Subject	talk
11:40 - 12:00	Freeview demonstration	demo
12:00 - 1:00	**Lunch** (Suggestions for where to eat)	--
1:00 - 2:00	Interaction with Individual Subject Data Tutorial	tutorial
2:00 - 2:30	* MRI Acquisition Methods	talk

Note about tutorials: we have many people with different background who will help. Whoever comes over first will either be able to answer your question(s), or will find someone who can

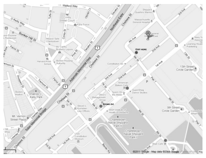
Search on YouTube for the FreeSurfer channel!

Food and such



12:20	Registration		
12:20 - 1:20	**Lunch** (Suggestions for where to eat)	--	--
12:35 -	*Optional Lunch Talk- A Non-physicist's Intro to MR*	*talk*	*Dylan Tisdall*

Cafeteria in main building (Building 149)



Morning coffee and "breakfast" – muffins, bagels, fruit
Afternoon coffee and some snacks

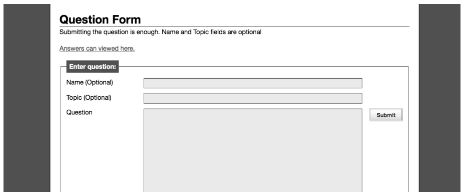
Tuesday evening socializing at Boston Beer Works

To Caffeinate or not to Caffeinate?

Please don't spill coffee (or anything else!) on the laptops. If you do, please be prepared to fund a replacement!

Post Your Questions!

http://surfer.nmr.mgh.harvard.edu/cgi-bin/fsurfer/questions.cgi

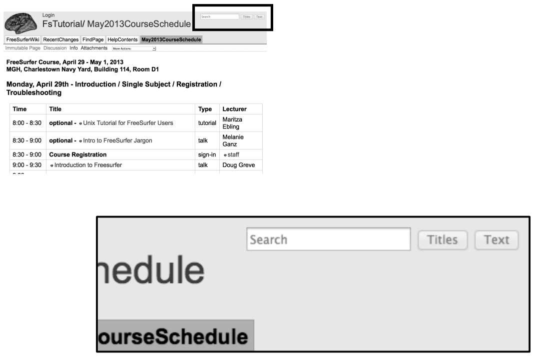


Question Form

Submitting the question is enough. Name and Topic fields are optional

Answers can viewed here.

Search for Answers



FreeSurfer Course, April 29 - May 1, 2013
MGH, Charlestown Navy Yard, Building 114, Room D1

Monday, April 29th - Introduction / Single Subject / Registration / Troubleshooting

Time	Title	Type	Lecturer
8:00 - 8:30	**optional -** Unix Tutorial for FreeSurfer Users	tutorial	Maritza Ebling
8:30 - 9:00	**optional -** Intro to FreeSurfer Jargon	talk	Melanie Ganz
8:30 - 9:00	**Course Registration**	sign-in	staff
9:00 - 9:30	Introduction to Freesurfer	talk	Doug Greve

What is FreeSurfer?

- Neuroimaging analysis software package
  - Open Source
- Detailed characterization of anatomy
  - Cortex – thickness, folding patterns, ROIs
  - Subcortical – structure boundaries
  - Hippocampal subfields
  - Longitudinal analysis – detect changes
- Statistical tools (GLM, LME, …), group comparison
- Multi-modal integration
  - fMRI (task, rest, retinotopy)
  - DWI Tractography
  - PET

What is FreeSurfer?

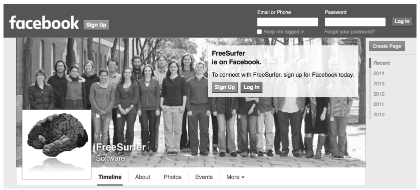
… popular ...

Total # licenses distributed as of July: 25,214

What is FreeSurfer?

… social ...

https://www.facebook.com/FreeSurferMRI



FreeSurfer
is on Facebook.

To connect with FreeSurfer, sign up for Facebook today.

Facebook, Twitter, LinkedIn

Outline

- Anatomical Analysis
  - Surface-based (Cortex)
  - Volume-based
- Multi-modal integration
  - DWI/Tractography
  - fMRI

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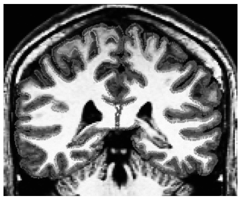
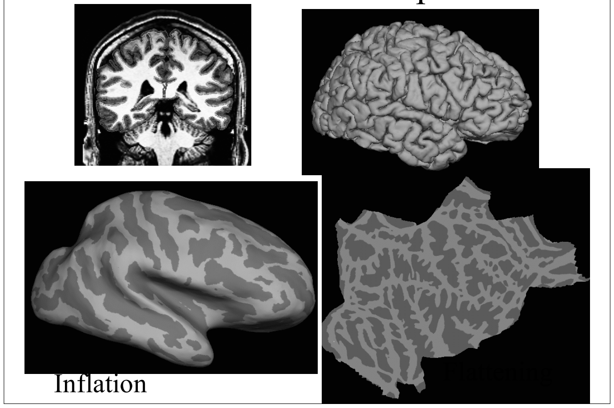
Cortex



- Outer layer of gray matter
- 1-5mm thick
- Highly folded
- 2 Dimensional, embedded in 3D
- Function follows the surface
  - Visualization
  - Spatial Smoothing
  - Inter-subject Registration

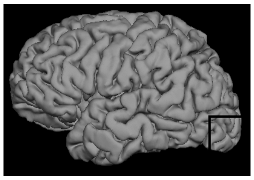
2D Surface in 3D Space



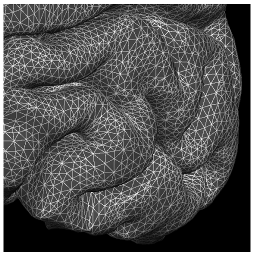
Inflation

Flattening

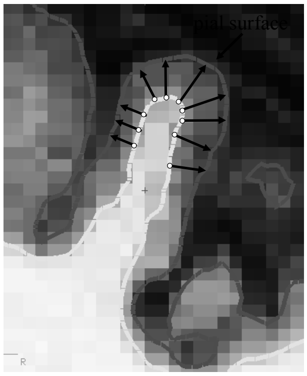
Surface Model



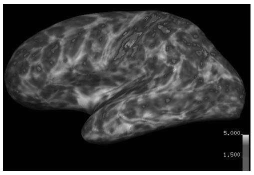
- Triangle Mesh (“Finite Element”)
- Vertex = point of triangles
- Neighborhood
- XYZ at each vertex
- Triangles/Faces ~ 300,000
- Area, Distance
- Curvature, Thickness
- Movable



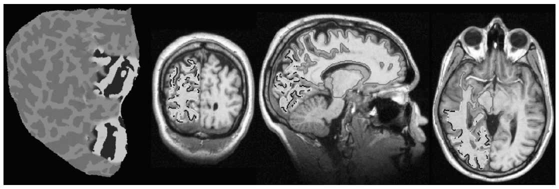
Cortical Thickness



- Shortest distance between white and pial surfaces.
- 1-5mm in healthy subjects



Function Follows the Surface



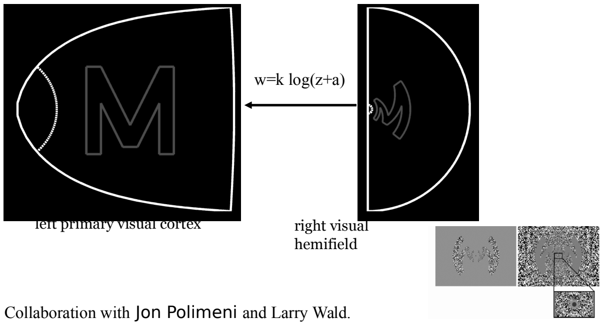
- Visual areas mapped using fMRI retinotopy
- Pattern is clear on the surface, but lost in the volume

From (Sereno et al, 1995, Science).

What Can One Do With A Surface Model?

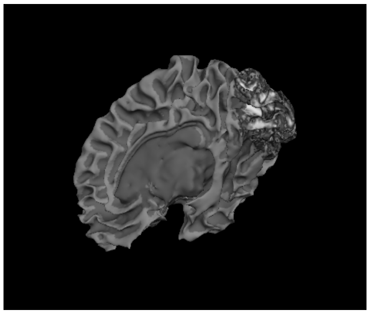
goal: use model to imposed desired activity pattern on V1

desired shape of activity pattern required shape of stimulus



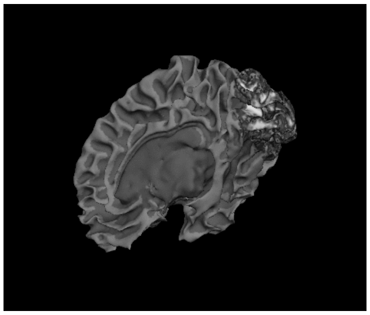
Collaboration with Jon Polimeni and Larry Wald.

Tangential Resolution Measured with Surface-based Analysis



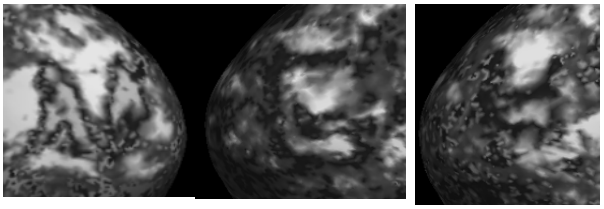
Collaboration with Jon Polimeni and Larry Wald. Polimeni, et al, 2010, NI.

Tangential Resolution Measured with Surface-based Analysis



Collaboration with Jon Polimeni and Larry Wald. Polimeni, et al, 2010, NI.

NeuroMarketing!



Aim 1 of our NCRR Center Grant, spelling:

"MGH Center for Functional Neuroimaging Technologies; and NCRR Center for Research Resources."

(just kidding)

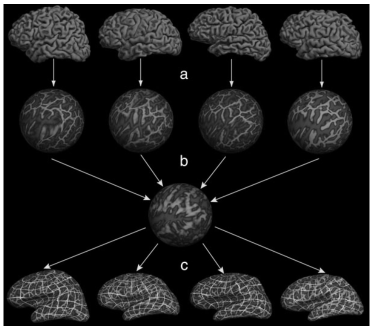
Thanks to Larry Wald for this slide.

Problems with Affine (12 DOF) Registration

Subject 1

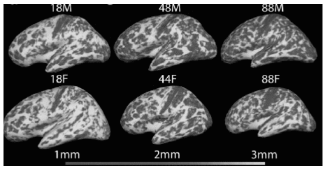
Subject 2 aligned with Subject 1 (Subject 1's Surface)

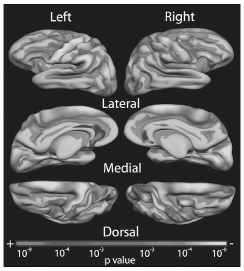
A Surface-Based Registration

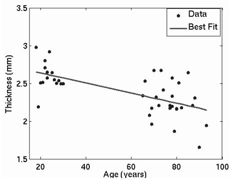


Common space for group analysis (like Talairach) "fsaverage"

Anatomical Study: Aging

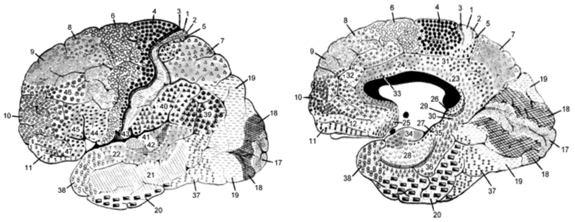






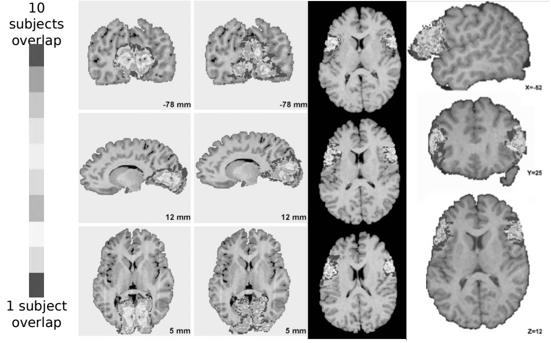
Salat, et al, 2004, Cerebral Cortex

Surface-based Registration Performance



Brodmann, 1909

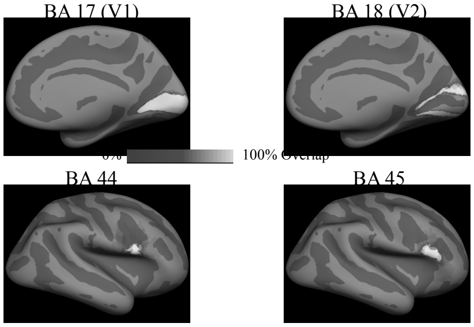
Predicting Brodmann Areas: Talairach Coordinates



BA17 (V1) BA18 (V2) BA44 (Broca 's) BA45
(Broca's)

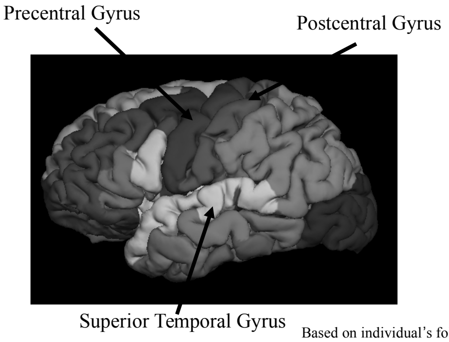
(Amunts et al, 2000, 2004)

Predicting Brodmann Areas from Folding Patterns



Fischl, et al, 2007. Thanks to Katrin Amunts, Karl Zilles and Hartmut Mohlberg for the data, and to Niranjini Rajendran and Evelina Busa for the analysis.

Automatic Gyral Segmentation



Based on individual's folding pattern

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  - Surface-based (Cortex)
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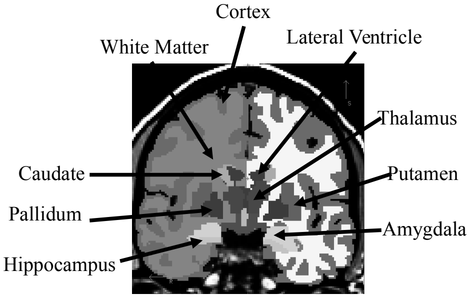
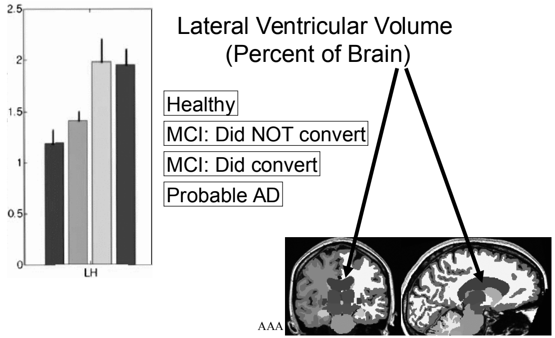
Volumetric Segmentation (aseg)



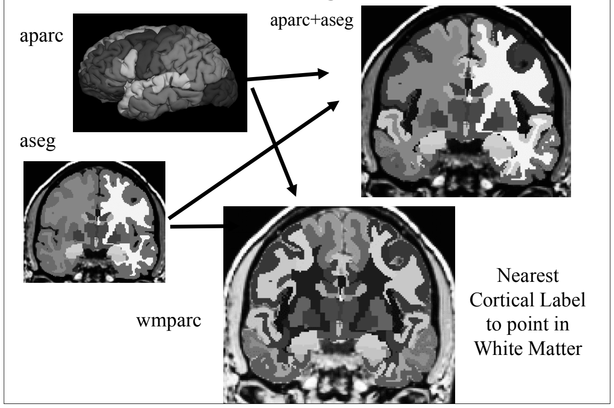
Not Shown:
Nucleus Accumbens
Cerebellum

ROI Volume Study



Fischl, et al, 2002, Neuron

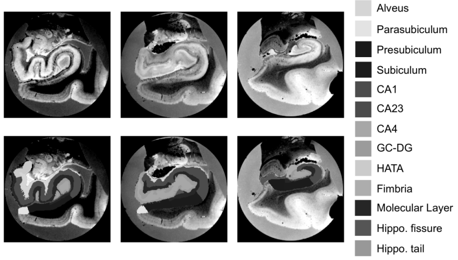
Combined Segmentation



Ex vivo MRI of hippocampal subfields

Resolution as high as 0.1 mm isotropic

- Allows precise manual tracing of hippocampal subfields.
- The delineation only relies on geometry for subdividing the CA.



Joint work with J. Eugenio Iglesias, Koen van Leemput and Jean Augustinack

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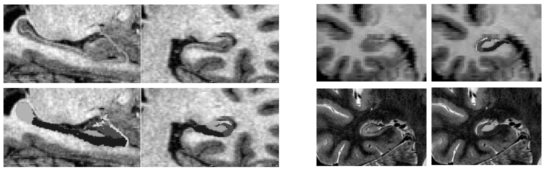
Automated Segmentation

We use the atlas as a prior, and connect it to the image through a Gaussian likelihood term for each label.

- This makes the segmentation sequence-independent.

0.6 mm isotropic T1 (Winterburn et al.)

1 mm T1 + 0.4x0.4x2 mm T2 (ADNI)



Joint work with J. Eugenio Iglesias, Koen van Leemput and Jean Augustinack

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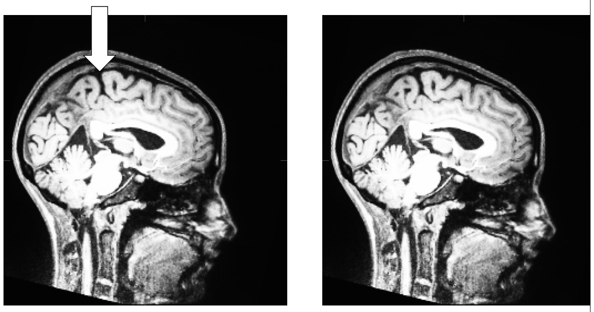
Robust Registration

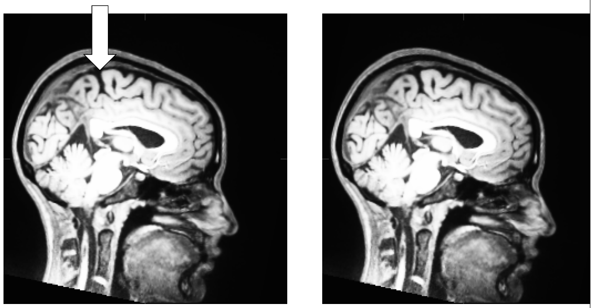


Target

Target

Reuter et al, 2010 NeuroImage

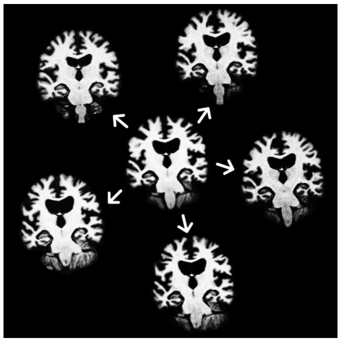
Robust Registration



Registered Src correlation ratio Registered Src Robust

Reuter et al, 2010 NeuroImage

Longitudinal Processing



1. Create unbiased subject template (iterative registration to median)
2. Process template
3. Initialize time points
4. Let it evolve there

- Avoid Bias: All time points are treated the same
- Increases sensitivity and reliability!

Reuter et al. OHBM 2010, NeuroImage 2011 & 2012

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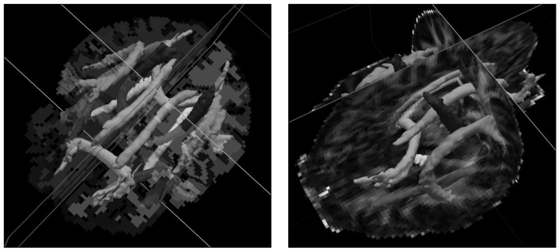
Tractography with TRACULA

(TRActs Constrained by the Underlying Anatomy)



- Completely automated modeling of 18 major fascicles
- Uses prior probabilistic information on the anatomical structures that each fascicle goes through or next to

Collaboration with Anastasia Yendiki, Lilla Zöllei, Saad Jbabdi, Tim Behrens and Jean

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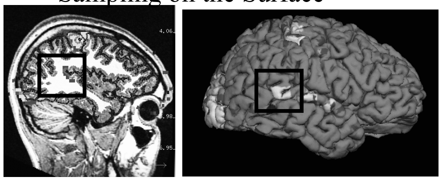
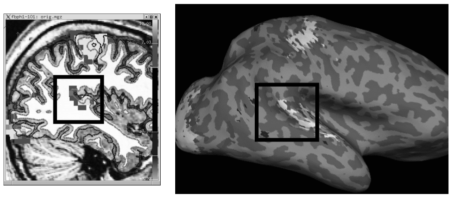
  - fMRI – task

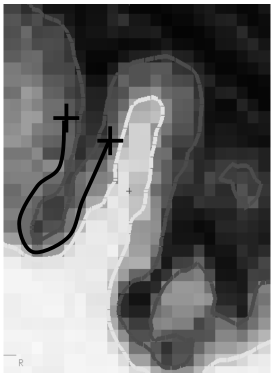
Sampling on the Surface



15 sec ‘ON’, 15 sec ‘OFF’
- Flickering Checkerboard
- Auditory Tone
- Finger Tapping

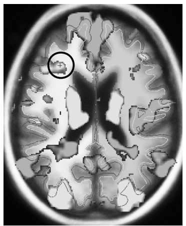


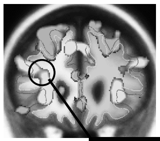
Spatial Smoothing



- 5 mm apart in 3D
- 25 mm apart on surface!
- Kernel much larger
- Averaging with other tissue types (WM, CSF)
- Averaging with other functional areas

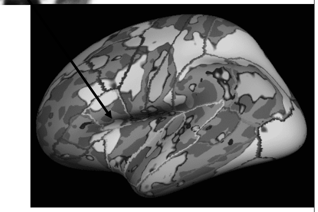
Group fMRI Analysis: Volume vs Surface

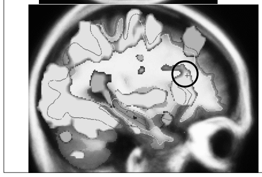




Affine registration to MNI305

5mm volume smoothing vs.
10mm surface smoothing

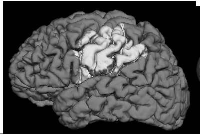




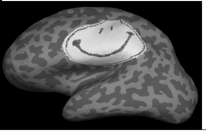
What is FreeSurfer?

- Cortical extraction and labeling
- Subcortical Segmentation
- Surface-based Inter-subject Registration
- Fully automated
- Multi-modal integration

Use FreeSurfer

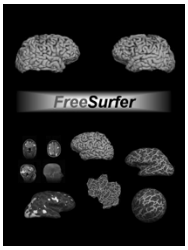


Be Happy

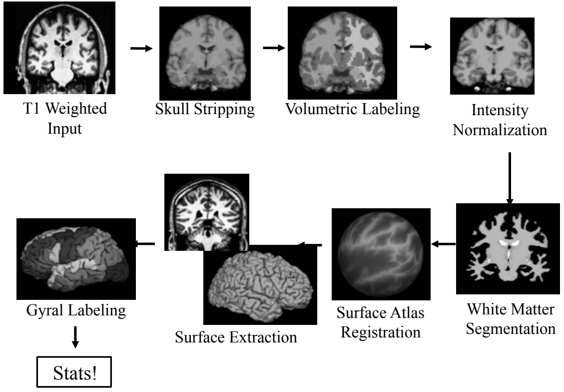


Anatomical Analysis with FreeSurfer

surfer.nmr.mgh.harvard.edu

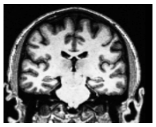


Processing Stream Overview



Input: T1 Weighted Image

- T1 Contrast: white matter brighter than gray matter
- ~1mm^3 (no more than 1.5mm)
- Higher resolution may be worse!
- Full Brain
- Usually one acquisition is ok
- MPRAGE or SPGR
- 1.5T or 3T
- 7T might have problems
- Subject age > 5 years old
- Brain has no major problems (ie, tumors, parts missing)
- Non-human primates possible

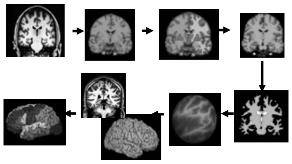


More MRI Pulse Sequence Parameter Details:
http://www.nmr.mgh.harvard.edu/~andre

Fully Automated Reconstruction*

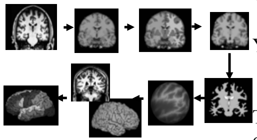
```
recon-all   –i  file.dcm   –subject  bert   –all
```

* "Reconstruction" here refers to cortical reconstruction, not k-space reconstruction.



Fully Automated Reconstruction

```
recon-all
  –i  file.dcm
  –subject  bert
  –all
```



file.dcm is a single DICOM file from the T1 MRI series.

If you have more than one T1, then use:
–i file1.dcm –i file2.dcm

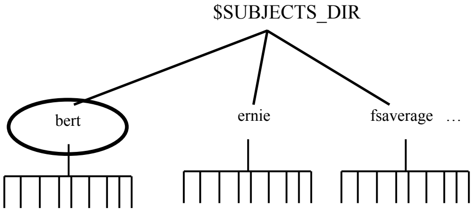
You can use NIFTI as well with
–i file.nii

To get a list of acquisitions:
dcmunpack –src /path/to/dicoms

Fully Automated Reconstruction

```
recon-all
  –i  file.dcm
  –subject  bert
  –all
```

"bert" is the "name" of the subject
Creates a folder in $SUBJECTS_DIR
All output goes in this folder (~400MB)
Other subjects in $SUBJECTS_DIR



setenv SUBJECTS_DIR /path/to/space

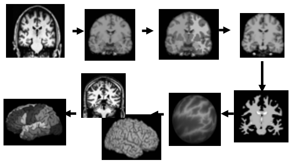
Fully Automated Reconstruction

```
recon-all
  –i  file.dcm
  –subject  bert
  –all
```

-all   means to do everything!

Can take 10-20 hours

Later, we will show you how to run subsets of the processing stream to make it faster when correcting errors.



Individual Steps

Volumetric Processing Stages (subjid/mri):

1. Motion Cor, Avg, Conform (orig.mgz)
2. Non-uniform inorm (nu.mgz)
3. Talairach transform computation (talairach/talairach.xfm)
4. Intensity Normalization 1 (T1.mgz)
5. Skull Strip (brainmask.mgz)

6. EM Register (linear volumetric registration)
7. CA Intensity Normalization (norm.mgz)
8. CA Non-linear Volumetric Registration
9. CA Label (Volumetric Labeling) (aseg.mgz)

10. Intensity Normalization 2 (T1.mgz)
11. White matter segmentation (wm.mgz)
12. Edit WM With ASeg
13. Fill and cut (filled.mgz)

Surface Processing Stages (subjid/surf):

14. Tessellate (?h.orig.nofix)
15. Smooth1
16. Inflate1
17. Sphere (?h.qsqhere)
18. Automatic Topology Fixer (?h.orig)
19. Final Surfs (?h.white ?h.pial ?.thickness)
20. Smooth2 (?h.smoothwm)
21. Inflate2 (?h.inflated)
22. Aseg Statistics (stats/aseg.stats)
23. Cortical Ribbon Mask (?h.ribbon.mgz)

24. Spherical Morph
25. Spherical Registration (?h.sphere.reg)
26. Map average curvature to subject
27. Cortical Parcellation (Labeling)
28. Cortical Parcellation Statistics
29. Cortical Parcellation mapped to Aseg
30. White Matter Parcellation (wmparc.mgz)

`recon-all  -help`

Note: ?h.orig means lh.orig or rh.orig

Upon Completion…

$SUBJECTS_DIR/bert

scripts   mri   surf   label   stats

recon-all –i file.dcm –subject bert –all   ~400MB

Upon Completion…

bert

scripts   mri   surf   label   stats

recon-all.log

recon-all.done

```
limiting computations to label ./rh.entorhinal_exvivo.label.
reading volume /autofs/cluster/freesurfer/test/dng/v5.3/b40/045/mri/wm.mgz...
reading input surface /autofs/cluster/freesurfer/test/dng/v5.3/b40/045/surf/rh.white...
reading input pial surface /autofs/cluster/freesurfer/test/dng/v5.3/b40/045/surf/rh.pial...
reading input white surface /autofs/cluster/freesurfer/test/dng/v5.3/b40/045/surf/rh.white...
INFO: assuming MGZ format for volumes.

table columns are:
    number of vertices
    total surface area (mm^2)
    total gray matter volume (mm^3)
    average cortical thickness +- standard deviation (mm)
    integrated rectified mean curvature
    integrated rectified Gaussian curvature
    folding index
    intrinsic curvature index
    structure name

  236    152    759  3.117 0.598     0.141     0.035        3     0.4  ./rh.entorhinal_exvivo.label

#-----------------------------------------

Started at Fri Apr 26 19:18:47 EDT 2013
Ended   at Sat Apr 27 12:07:26 EDT 2013
#@#%# recon-all-run-time-hours 16.811
recon-all -s 045 finished without error at Sat Apr 27 12:07:26 EDT 2013
[t:0:~-> 
```

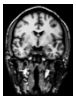
Just because it finishes "without error" does not mean that everything is ok!

Send us recon-all.log when you have problems!
freesurfer@nmr.mgh.harvard.edu

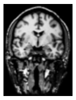
Upon Completion…

bert

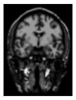
scripts   mri   surf   label   stats



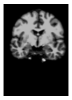
rawavg.mgz



orig.mgz



T1.mgz



brainmask.mgz

wm.mgz

aseg.mgz

others: nu.mgz, norm.mgz, wmparc.mgz, aparc+aseg.mgz, ribbon.mgz

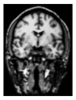
mgz = "compressed mgh" format (like nifti) unique to FreeSurfer

---

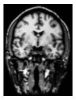
Upon Completion…

bert

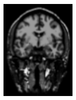
scripts   mri   surf   label   stats



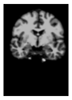
rawavg.mgz



orig.mgz



T1.mgz



brainmask.mgz

wm.mgz

aseg.mgz

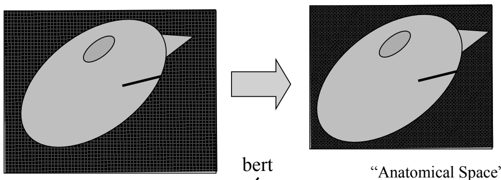
Native Anatomical Space
eg, 1x1x1.2mm^3 , 256x256x128

"Conformed" Anatomical Space
1x1x1mm^3 , 256x256x256

Conform Step

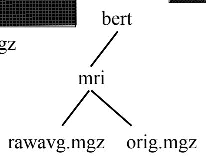
Native Anatomical Space
1x1x1.1mm, 256x256x128, Sag

Conformed Anatomical Space
1x1x1mm, 256x256x256, Cor

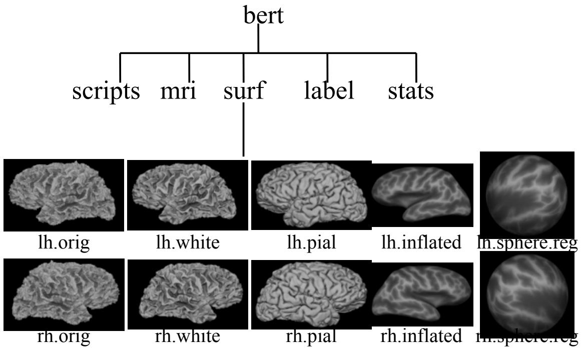


rawavg.mgz

"Anatomical Space"
orig.mgz
Surfaces
Parcellations
Segmentations

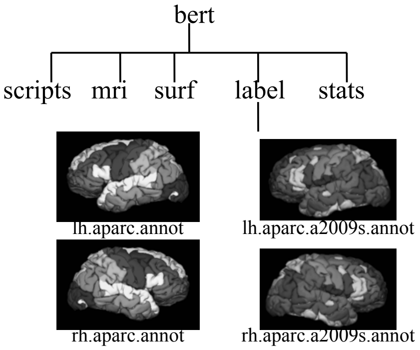


Upon Completion…



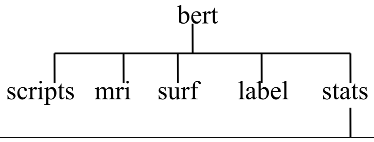
lh.thickness and rh.thickness, ?h.curv, ?h.sulc

Upon Completion…



Desikan/Killiany Atlas   Destrieux Atlas

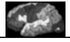
Upon Completion…



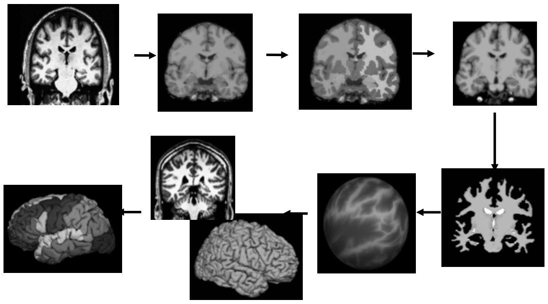
aseg.stats – subcortical volumetric stats
wmparc.stats – white matter segmentation volumetric stats
lh.aparc.stats – left hemi Desikan/Killiany surface stats
rh.aparc.stats – right hemi Desikan/Killiany surface stats
lh.aparc.a2009.stats – left hemi Destrieux
rh.aparc.a2009.stats – right hemi Destrieux

stats files are text files with summary information, eg:

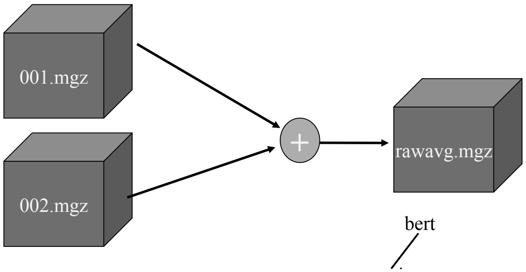
- volume of left amygdala
- average thickness in superior temporal gyrus

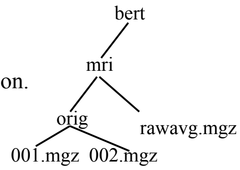


Some of the Processing Steps…



Motion Correction and Averaging





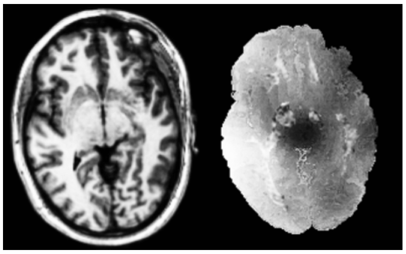
Does not change native resolution.
Usually only need one.

Talairach Transform

- Computes 12 DOF transform matrix
- Does NOT resample
- MNI305 template
- Mostly used to report coordinates

bert
scripts mri surf label stats
transforms
talairach.xfm → text file with matrix

Intensity Bias

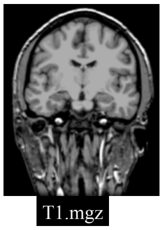


bert
mri
T1.mgz

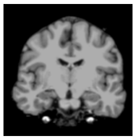
- Left side of the image much brighter than right side
- Worse with many coils
- Makes gray/white segmentation difficult

Skull Strip

- Removes all non-brain
  - Skull, Eyes, Neck, Dura
- brainmask.mgz (cf, brain.mgz)



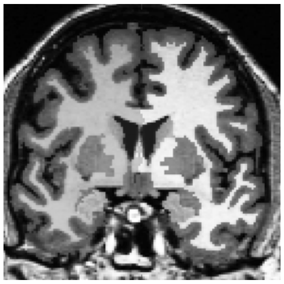
T1.mgz



brainmask.mgz

bert
mri
brainmask.mgz

Automatic Volume Labeling



ASeg Volume

- Used to fill in subcortical structures for creating subcortical mass
- Useful in its own right
- aseg.mgz
- More in ROI Talk

bert
mri
aseg.mgz

Atlas: $FREESURFER_HOME/average/RB_all_2008-03-26

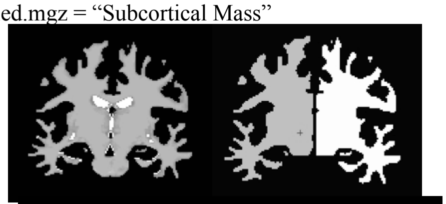
“White Matter” Segmentation

- Separates white matter from everything else
- Uses aseg to “fill in” subcortical structures
- Cerebellum removed, brain stem still there
- wm.mgz -- “wm” not a very good name!

bert
mri
wm.mgz

Fill and Cut (Subcortical Mass)

- Fills in any holes.
- Removes any islands
- Removes brain stem
- Separates hemispheres (each hemi has different value)
- filled.mgz = “Subcortical Mass”

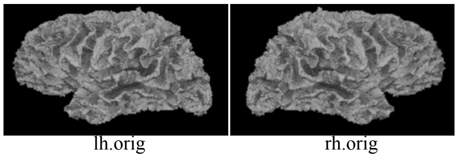


WM Volume (wm.mgz) Filled Volume (filled.mgz) (Subcortical Mass)

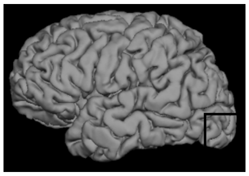
Surface Extraction

- Hemispheres separated
- Fit to wm.mgz
- 1mm resolution
- Rough, jagged

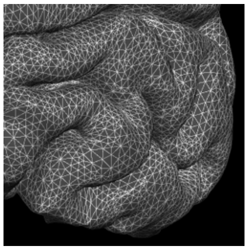
bert
surf
lh.orig
rh.orig



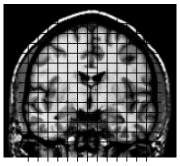
Surface Model



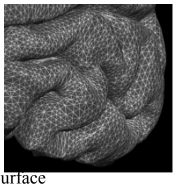
- Mesh (“Finite Element”)
- Vertex = point of triangles
- Neighborhood
- XYZ at each vertex
- Triangles/Faces ~ 300,000
- Vertices ~ 140,000
- Area, Distance
- Curvature, Thickness



Volume vs Surface Model



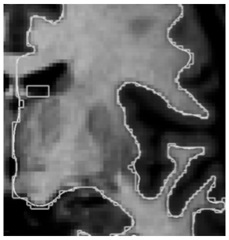
Volume
- uniform grid
- voxel is an intersection of grid lines
- columns, rows, slices
- voxel size/distance
- voxel assigned a value
- XYZ



Surface
- NON-uniform grid
- vertex is an intersection of triangles
- each vertex has an index
- distance between vertices ~1mm
- vertex assigned a value
- XYZ

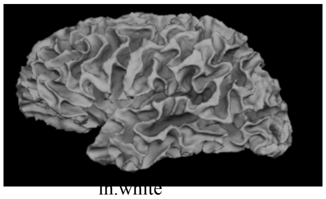
Vector of vertex values (~140,000)

White Matter Surface



- Nudge orig surface
- Follow T1 intensity gradients
- Smoothness constraint
- Vertex identity preserved

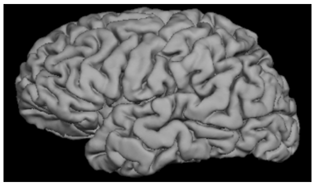
—— orig surface
—— white surface



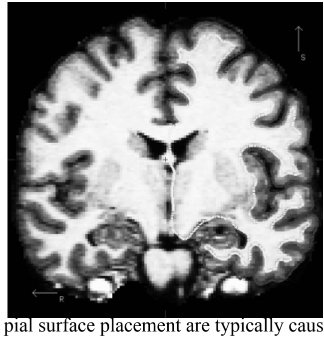
lh.white
rh.white

Pial Surface

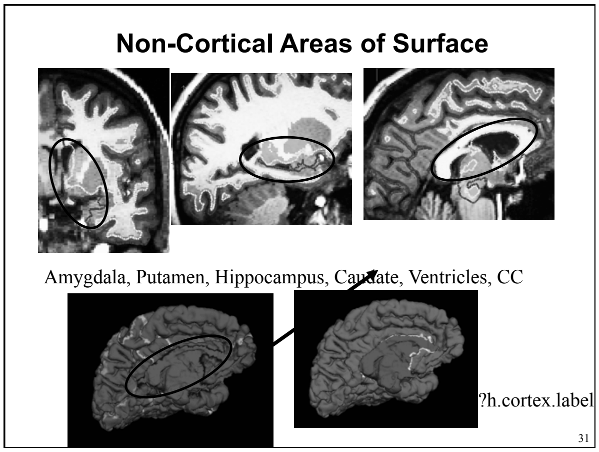
- Nudge white surface
- Follow T1 intensity gradients
- Vertex identity preserved



Pial surf grows from white surf



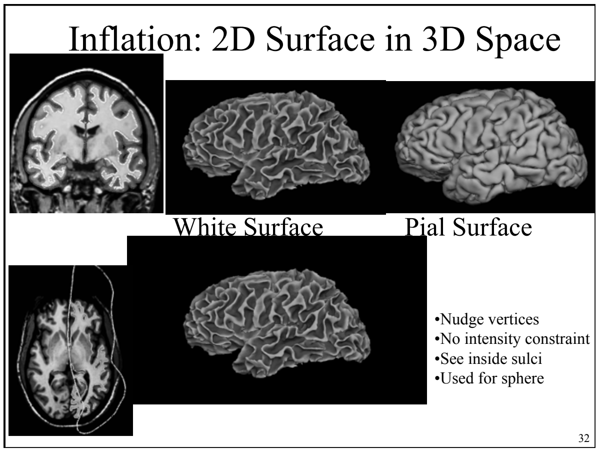
Errors in pial surface placement are typically caused by underlying errors in the white matter placement, and can be corrected by interventions such as white matter control points.



Non-Cortical Areas of Surface

Amygdala, Putamen, Hippocampus, Caudate, Ventricles, CC

?h.cortex.label

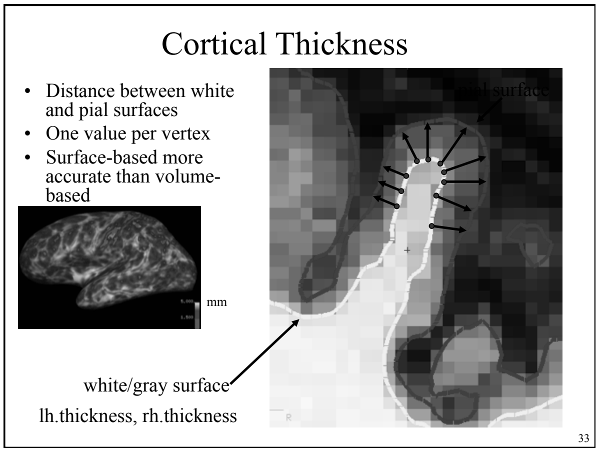


Inflation: 2D Surface in 3D Space

White Surface

Pial Surface

- Nudge vertices
- No intensity constraint
- See inside sulci
- Used for sphere

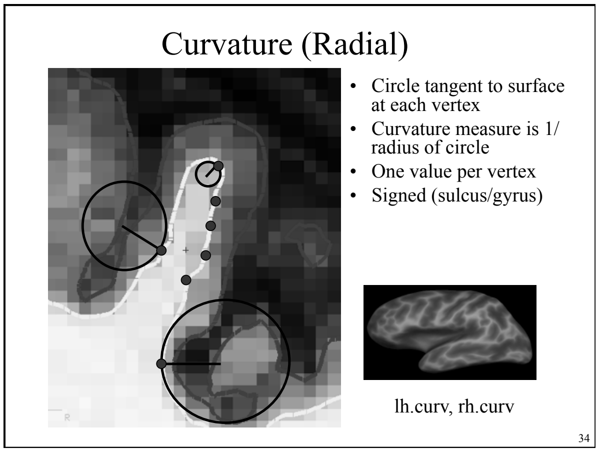


Cortical Thickness

- Distance between white and pial surfaces
- One value per vertex
- Surface-based more accurate than volume-based

white/gray surface

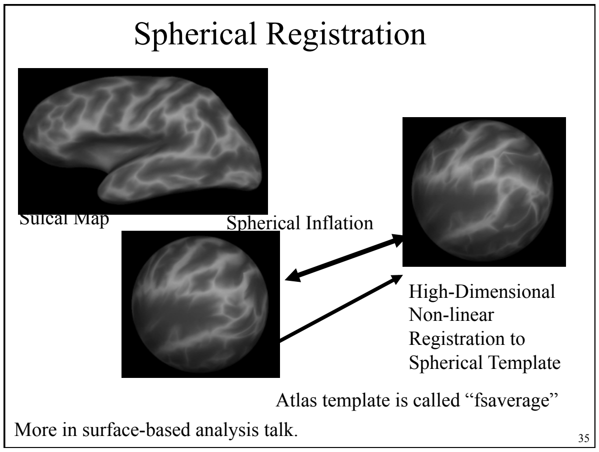
lh.thickness, rh.thickness



Curvature (Radial)

- Circle tangent to surface at each vertex
- Curvature measure is 1/radius of circle
- One value per vertex
- Signed (sulcus/gyrus)

lh.curv, rh.curv



Spherical Registration

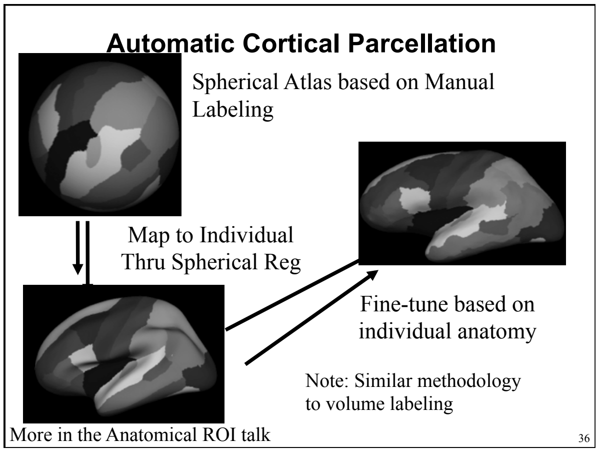
Sulcal Map

Spherical Inflation

High-Dimensional
Non-linear
Registration to
Spherical Template

Atlas template is called “fsaverage”

More in surface-based analysis talk.



Automatic Cortical Parcellation

Spherical Atlas based on Manual Labeling

Map to Individual Thru Spherical Reg

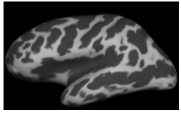
Fine-tune based on individual anatomy

Note: Similar methodology to volume labeling

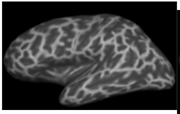
More in the Anatomical ROI talk

Surface Overlays

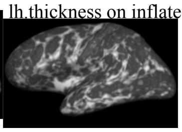
lh.sulc on inflated



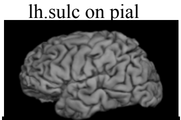
lh.curv on inflated



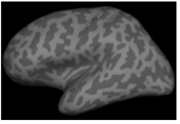
lh.thickness on inflated



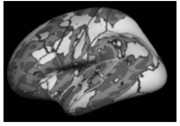
lh.sulc on pial



lh.curv on inflated



fMRI on inflated



lh.aparc.annot on inflated

- Value for each vertex
- Color indicates value
- Color: gray, red/green, heat, color table
- Rendered on any surface
- fMRI/Stat Maps too

ROI Summaries:

$SUBJECTS_DIR/bert/stats
 aseg.stats – volume summaries
 ?h.aparc.stats – desikan/killiany surface summaries
 ?h.aparc.a2009s.stats – destrieux surface summaries
 wmparc.stats – white matter parcellation

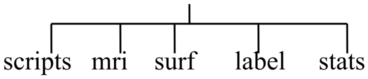
```
Index SegId NVoxels Volume_mm3 StructName normMean normStdDev normMin normMax normRange
 1  1        0        0.0  Left-Cerebral-Exterior          0.0000    0.0000   0.0000    0.0000      0.0000
 2  2   265295   265295.0  Left-Cerebral-White-Matter    106.6763    8.3842  35.0000  169.0000    134.0000
 3  3   251540   251540.0  Left-Cerebral-Cortex           81.8395   10.2448  29.0000  170.0000    141.0000
 4  4     7347     7347.0  Left-Lateral-Ventricle         42.5800   12.7435  21.0000   90.0000     69.0000
 5  5      431      431.0  Left-Inf-Lat-Vent              66.2805   11.4191  30.0000   95.0000     65.0000
 6  6        0        0.0  Left-Cerebellum-Exterior        0.0000    0.0000   0.0000    0.0000      0.0000
….
```

Routines to generate spread sheets of group data

- asegstats2table --help
- aparcstats2table --help

More info in Anatomical ROI talk.

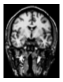
Upon Completion of recon-all



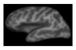
$SUBJECTS_DIR /bert

scripts mri surf label stats

recon-all.log



orig.mgz



lh.inflated

lh.aparc.annot

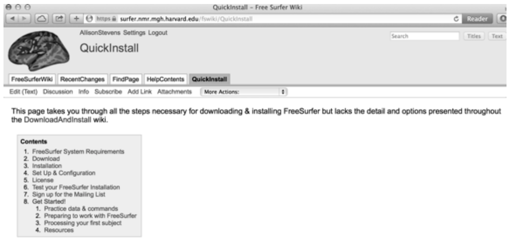
aseg.stats

recon-all –i file.dcm –subject bert –all

Getting FreeSurfer

- surfer.nmr.mgh.harvard.edu
  - Register
  - Download
  - Mailing List
- Wiki: surfer.nmr.mgh.harvard.edu/fswiki
- Platforms:
  - Linux
  - Mac
  - Windows (VirtualBox)
- Installed in $FREESURFER_HOME

Download & Install



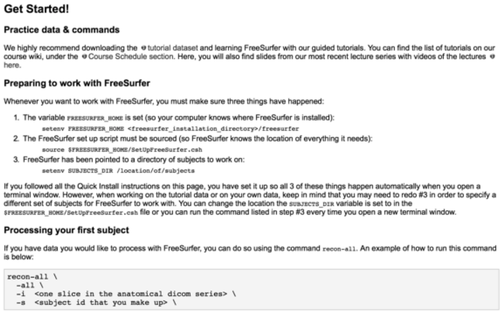
QuickInstall

This page takes you through all the steps necessary for downloading & installing FreeSurfer but lacks the detail and options presented throughout the DownloadAndInstall wiki.

Contents

1. FreeSurfer System Requirements
2. Download
3. Installation
4. Set Up & Configuration
5. License
6. Test your FreeSurfer Installation
7. Sign up for the Mailing List
8. Get Started!
   1. Practice data & commands
   2. Preparing to work with FreeSurfer
   3. Processing your first subject
   4. Resources

What to do next



Get Started!

Practice data & commands

We highly recommend downloading the tutorial dataset and learning FreeSurfer with our guided tutorials. You can find the list of tutorials on our course wiki, under the Course Schedule section. Here, you will also find slides from our most recent lecture series with videos of the lectures here.

Preparing to work with FreeSurfer

Whenever you want to work with FreeSurfer, you must make sure three things have happened:

1. The variable `FREESURFER_HOME` is set (so your computer knows where FreeSurfer is installed):
   ```
   setenv FREESURFER_HOME <freesurfer_installation_directory>/freesurfer
   ```
2. The FreeSurfer set up script must be sourced (so FreeSurfer knows the location of everything it needs):
   ```
   source $FREESURFER_HOME/SetUpFreeSurfer.csh
   ```
3. FreeSurfer has been pointed to a directory of subjects to work on:
   ```
   setenv SUBJECTS_DIR /location/of/subjects
   ```

If you followed all the Quick Install instructions on this page, you have set it up so all 3 of these things happen automatically when you open a terminal window. However, when working on the tutorial data or on your own data, keep in mind that you may need to redo #3 in order to specify a different set of subjects for FreeSurfer to work with. You can change the location the `SUBJECTS_DIR` variable is set to in the `$FREESURFER_HOME/SetUpFreeSurfer.csh` file or you can run the command listed in step #3 every time you open a new terminal window.

Processing your first subject

If you have data you would like to process with FreeSurfer, you can do so using the command `recon-all`. An example of how to run this command is below:

```
recon-all \
  -all \
  -i  <one slice in the anatomical dicom series> \
  -s  <subject id that you make up> \
```

Getting Answers

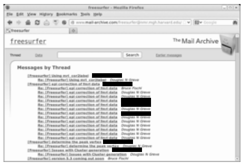
Wiki

Welcome

Welcome to the **FreeSurferWiki**. The FreeSurferWiki is the central documentation and download source for FreeSurfer, a software application developed at the Martinos Center for Biomedical Imaging by the Laboratory for Computational Neuroimaging.

FreeSurfer is a set of tools for analysis and visualization of structural and functional brain imaging data. FreeSurfer contains a fully automatic structural imaging stream for processing cross sectional and longitudinal data.

Mail Archive



Messages by Thread

[Freesurfer] Using mri_cor2label [redacted]
Re: [Freesurfer] Using mri_cor2label Douglas N Greve
[Freesurfer] epi correction of fmri data [redacted]
Re: [Freesurfer] epi correction of fmri data Bruce Fischl
Re: [Freesurfer] epi correction of fmri data Douglas N Greve
Re: [Freesurfer] epi correction of fmri data Douglas N Greve
Re: [Freesurfer] epi correction of fmri data [redacted]
Re: [Freesurfer] epi correction of fmri data
Re: [Freesurfer] epi correction of fmri data Douglas N Greve
Re: [Freesurfer] epi correction of fmri data [redacted]
Re: [Freesurfer] epi correction of fmri data Douglas N Greve
Re: [Freesurfer] epi correction of fmri data Douglas N Greve
Re: [Freesurfer] epi correction of fmri data Douglas N Greve
Re: [Freesurfer] epi correction of fmri data Douglas N Greve
Re: [Freesurfer] epi correction of fmri data Douglas N Greve
Re: [Freesurfer] epi correction of fmri data Douglas N Greve
[Freesurfer] determine the peak vertex [redacted]
Re: [Freesurfer] determine the peak vertex Douglas N Greve
[Freesurfer] Issues with Cluster generation [redacted]
Re: [Freesurfer] Issues with Cluster generation Douglas N Greve
[Freesurfer] version 5.3 coming out soon Bruce Fischl

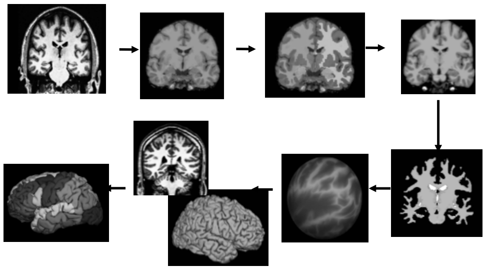
recon-all -help
mri_convert -help

$FREESURFER_HOME/docs

Send questions to:
freesurfer@nmr.mgh.harvard.edu

Overview

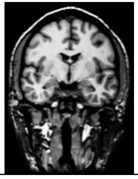
```
recon-all –i file.dcm –subject bert –all
```



Tutorial Tips

- Best not to run multiple instances of Freeview at the same time unless you have > 8GB RAM.
- If you are running a command in the foreground, you should not type additional commands in that terminal (command prompt will be missing)

Volume Viewer (Freeview) Radiological Orientation

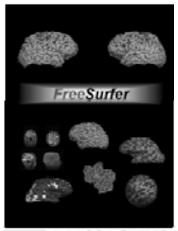


Right

Left

End of Presentation

Surface-based Analysis:
Intersubject Registration and Smoothing



MASSACHUSETTS
GENERAL HOSPITAL

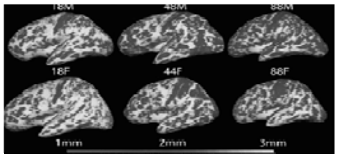
Outline

- Exploratory Spatial Analysis
- Coordinate Systems
  - 3D (Volumetric)
  - 2D (Surface-based)
- Intersubject registration
  - Volume-based
  - Surface-based
- Surface-based smoothing
- Surface-based clustering

Exploratory Spatial Analysis

- Don’t know where effect is going to be
- vs ROI analysis
- Analyze each voxel separately
- Create a map
- Find clusters

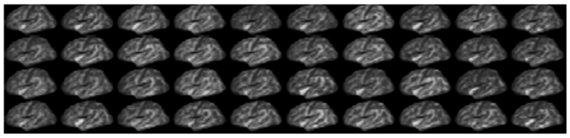
Aging Exploratory Analysis

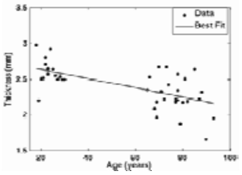


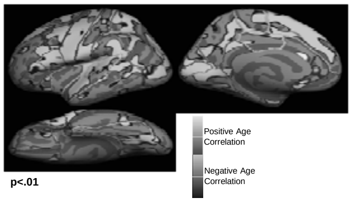
Cortical Thickness vs Aging
Salat, et al, 2004, Cerebral Cortex

Aging Thickness Study

N=40

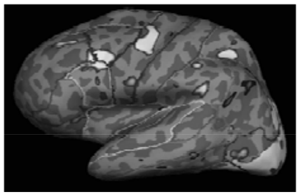






p<.01

Individual Exploratory Analysis



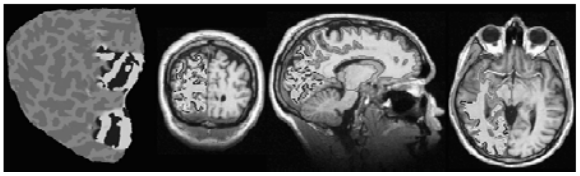
- fMRI Words-vs-Fixation
- Single subject (eg, presurgical planning or functional ROI)
- Outlines are FreeSurfer cortical ROIs
- Yellow and blue blobs are functional activation
- Activation does not lie cleanly within a predefined ROI

Exploratory Spatial Analysis

- Generally requires spatial smoothing of data to increase SNR
- For group analysis, requires that subjects’ brains be aligned to each other on a voxelwise basis.
- Neither needed for an ROI analysis
- Smoothing and intersubject registration can be performed in the volume or surface.

Why Is a Model of the Cortical Surface Useful?

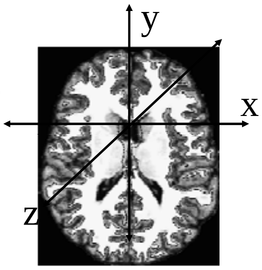
Local functional organization of cortex is largely 2-dimensional! Eg, functional mapping of primary visual areas:



From (Sereno et al, 1995, Science).

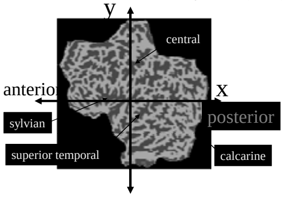
Coordinate Systems: 3D (Volumetric)

- 3D Coordinate System
  - XYZ
  - RAS (Right-Anterior-Superior)
  - CRS (Column-Row-Slice)
  - Origin (XYZ=0, eg, AC)
  - MR Intensity at each XYZ

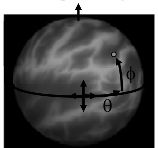


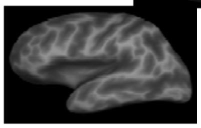
Coordinate Systems: 2D (Surface)

Sheet: 2D Coordinate System (X,Y)



Sphere: 2D Coordinate System
- Latitude and Longitude (θ, ϕ)
- Continuous, no cuts
- Value at each point (eg, thickness)



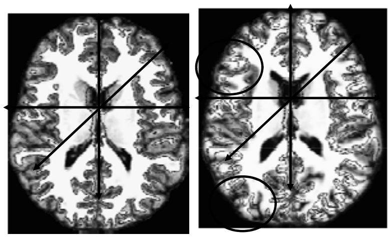


Curvature
- SULCUS (+)
- GYRUS (-)

Intersubject Registration

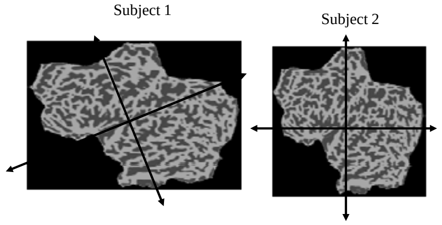
Volumetric Intersubject Registration

- Affine/Linear
  - Translate
  - Rotate
  - Stretch
  - Shear
  - (12 DOF)



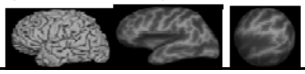
- Match Intensity, Voxel-by-Voxel
- Problems
- Can use nonlinear volumetric (cf CVS)

Surface-based Intersubject Registration

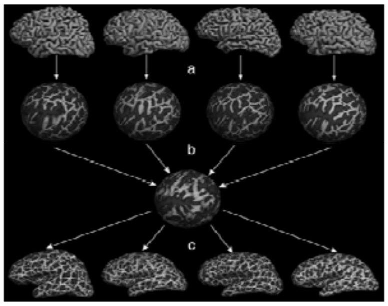


Curvature "Intensity"
- SULCUS (+)
- GYRUS (-)
- Codes folding pattern

- Translate, Rotate, Stretch, Shear (12 DOF)
- Match Curvature, Vertex-by-Vertex
- Nonlinear Stretching ("Morphing") allowed (area regularization)
- Actually done on sphere
- "Spherical Morph"



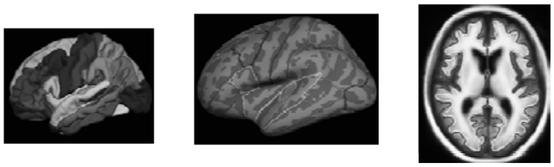
A Surface-Based Coordinate System



Common space for group analysis (like Talairach)

---

fsaverage



- Has "subject" folder like individual FS subjects
- "Buckner 40" subjects
- Default registration space
- MNI305 coordinates

?h.average.curvature.filled.buckner40.tif

Surface-based Intersubject Registration

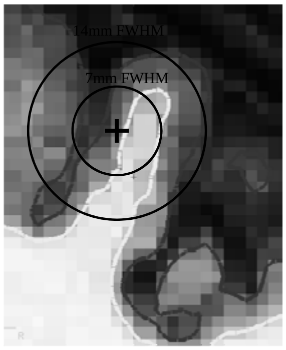
- Gray Matter-to-Gray Matter (it's all gray matter!)
- Gyrus-to-Gyrus and Sulcus-to-Sulcus
- Some minor folding patterns won't line up
- Fully automated, no landmarking needed
- Atlas registration is probabilistic, most variable regions get less weight.
- Done automatically in recon-all
- fsaverage

Spatial Smoothing

Why should you smooth?
- Might Improve CNR/SNR
- Improve intersubject registration

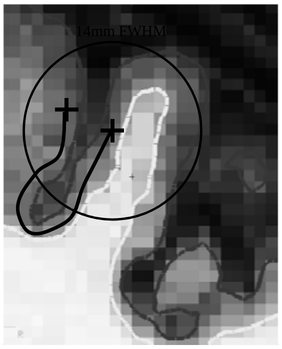
How much smoothing?
- Blob-size
- Typically 5-20 mm FWHM
- Surface smoothing more forgiving than volume-based

Volume-based Smoothing



- Smoothing is averaging of "nearby" voxels

Volume-based Smoothing

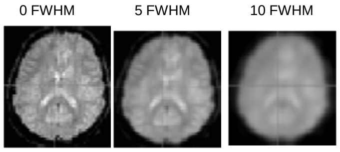


- 5 mm apart in 3D
- 25 mm apart on surface!
- Kernel much larger
- Averaging with other tissue types (WM, CSF)
- Averaging with other functional areas

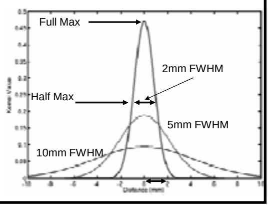
Spatial Smoothing

- Spatially convolve image with Gaussian kernel.
- Kernel sums to 1
- Full-Width/Half-max: FWHM = σ/sqrt(log(256))

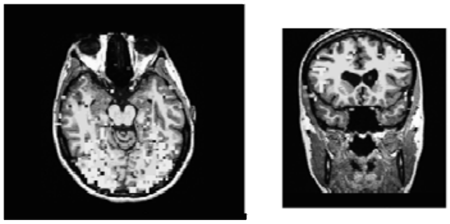
σ = standard deviation of the Gaussian



Full-Width/Half-max



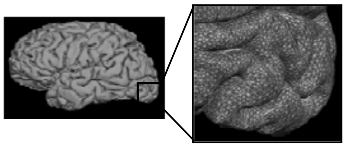
Effect of Smoothing on Activation



- Working memory paradigm
- FWHM: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20

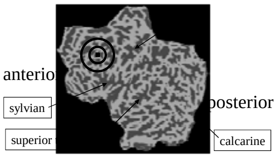
Surface-based Smoothing

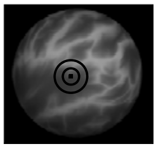
- Smoothing is averaging of nearby <u>vertices</u>



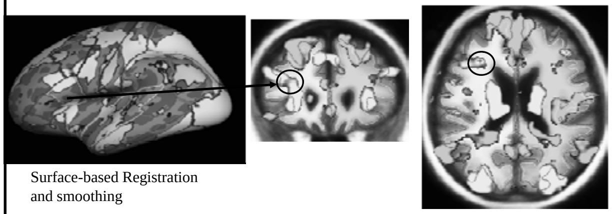
Sheet: 2D Coordinate System (X,Y)

Sphere: 2D Coordinate System (θ,ϕ)





Group fMRI Analysis: Volume vs Surface

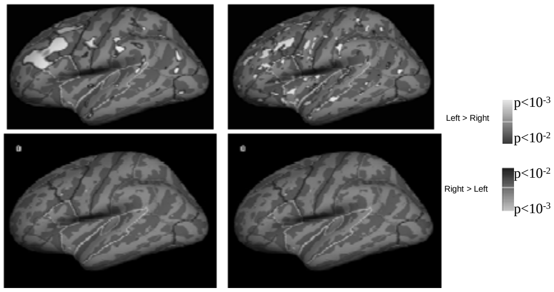


Surface-based Registration
and smoothing

Affine registration to MNI305
with volume smoothing

Probe-vs-Fixation. Data from Functional Biomedical Informatics Research Network (fBIRN)

$5HT_4$ BP Asymmetry Study (N=16)

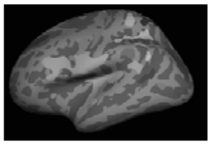


Surface Smoothing

Volume Smoothing

Surface-based Clustering

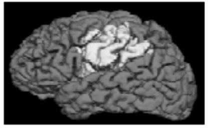
- A cluster is a group of connected (neighboring) vertices above threshold
- Neighborhood is 2D, not 3D
- Cluster has a size (area in mm^2)
- Reduced search space (corrections for multiple comparisons)



Summary

- Why Surface-based Analysis?
  - Function has surface-based organization
  - Inter-subject registration: anatomy, not intensity
  - Smoothing
  - Clustering
  - Like 3D, but 2D

Use FreeSurfer



Be Happy

- freesurfer.net

Working with FreeSurfer Regions-of-Interest (ROIs)

Outline

- Subcortical Segmentation
- Cortical Parcellation
- WM Segmentation
- Preparation/Analysis of Stats

FreeSurfer ROI Terminology

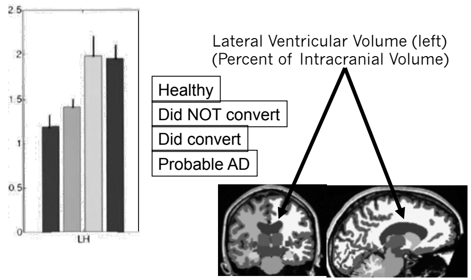
ROI = Region Of Interest

Volume/Image (Subcortical):
- Segmentation

Surface (Cortical):
- Parcellation/Annotation/Surface Segmentation
- Clusters, Masks (from sig.mgh, fMRI)
- Label you created

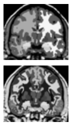
SUBCORTICAL AUTOMATIC SEGMENTATION (aseg)

ROI Volume Study



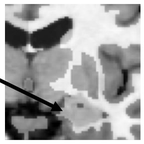
Fischl, et al, 2002, Neuron

Segmentation



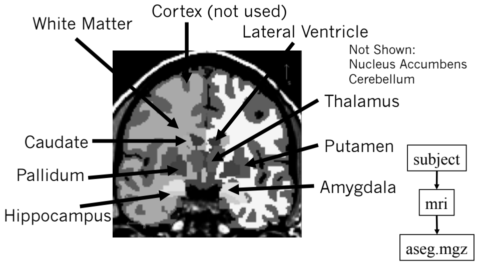
- Volume-style format (mgz, nii, nii.gz)
- Each voxel has one index (number ID)
- All voxels in the brain are labeled
- Index List found in color lookup table (LUT)
  - $FREESUFER_HOME/FreeSurferColorLUT.txt

    17 Left-Hippocampus   220 216 20   0
    Index = 17
    Name = Left-Hippocampus
    Red=220, Green=216, Blue=20 (out of 255)
    alpha = 0 (not really used)



- aseg.mgz, aparc+aseg.mgz, wmparc.mgz

Subcortical Segmentation (aseg)



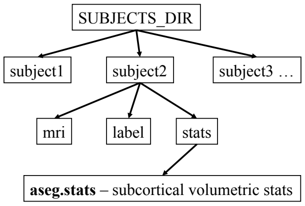
Whole Brain Segmentation: Automated Labeling of Neuroanatomical Structures in the Human Brain, Fischl et al. (2002). Neuron, 33:341-355.

Volumetric Segmentation Atlas Description

- 39 Subjects
- 14 Male, 25 Female
- Ages 18-87
  - Young (18-22): 10
  - Mid (40-60): 10
  - Old Healthy (69+): 8
  - Old Alzheimer's (68+): 11
- Siemens 1.5T Vision (Wash U)

Whole Brain Segmentation: Automated Labeling of Neuroanatomical Structures in the Human Brain, Fischl et al. (2002). Neuron, 33:341-355.

FreeSurfer Stats Outputs



SUBJECTS_DIR

subject1 subject2 subject3 …

mri label stats

aseg.stats – subcortical volumetric stats

created by *mri_segstats*

---

aseg.stats

```
Index SegId NVoxels Volume_mm3 StructName                        Mean      StdDev       Min        Max       Range
  1   4     5855     5855.0   Left-Lateral-Ventricle            37.7920   10.9705    20.0000    88.0000
68.0000
  2   5      245      245.0   Left-Inf-Lat-Vent                 56.4091    9.5906    26.0000    79.0000
53.0000
  3   7    16357    16357.0   Left-Cerebellum-White-Matter      91.2850    4.8989    49.0000   106.0000
57.0000
  4   8    60367    60367.0   Left-Cerebellum-Cortex            76.3620    9.5724    26.0000   135.0000
109.0000
  5  10     7460     7460.0   Left-Thalamus-Proper              91.3778    7.4668    43.0000   108.0000
65.0000
  6  11     3133     3133.0   Left-Caudate                      78.5801    8.2886    42.0000   107.0000
65.0000
  7  12     5521     5521.0   Left-Putamen                      86.9680    5.5752    66.0000   106.0000
40.0000
  8  13     1816     1816.0   Left-Pallidum                     97.7162    3.4302    79.0000   106.0000
27.0000
  9  14      852      852.0   3rd-Ventricle                     41.9007   11.8230    22.0000    69.0000
47.0000
 10  15     1820     1820.0   4th-Ventricle                     39.7053   10.5407    20.0000    76.0000
56.0000
 11  16    25647    25647.0   Brain-Stem                        85.2103    8.2819    38.0000   106.0000
68.0000
 12  17     4467     4467.0   Left-Hippocampus                  77.6346    7.5845    45.0000   107.0000
62.0000
 13  18     1668     1668.0   Left-Amygdala                     74.5104    5.8320    50.0000    94.0000
44.0000
 14  24     1595     1595.0   CSF                               52.1348   11.6113    29.0000    87.0000
58.0000
```

Index: nth Segmentation in stats file
SegId: index into lookup table
NVoxels: number of Voxels in segmentation
StructName: name of structure from LUT
Mean/StdDev/Min/Max/Range: intensity across ROI

---

aseg.stats Global Measures:
Cortical, Gray, White, Intracranial Volumes

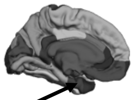
Also in aseg.stats header:

```
# Measure lhCortex, lhCortexVol, Left hemisphere cortical gray matter volume, 192176.447567, mm^3
# Measure rhCortex, rhCortexVol, Right hemisphere cortical gray matter volume, 194153.9526, mm^3
# Measure Cortex, CortexVol, Total cortical gray matter volume, 386330.400185, mm^3
# Measure lhCorticalWhiteMatter, lhCorticalWhiteMatterVol, Left hemisphere cortical white matter volume, 217372.890625, mm^3
# Measure rhCorticalWhiteMatter, rhCorticalWhiteMatterVol, Right hemisphere cortical white matter volume, 219048.187500,
    mm^3
# Measure CorticalWhiteMatter, CorticalWhiteMatterVol, Total cortical white matter volume, 436421.078125, mm^3
# Measure SubCortGray, SubCortGrayVol, Subcortical gray matter volume, 182006.000000, mm^3
# Measure TotalGray, TotalGrayVol, Total gray matter volume, 568336.400185, mm^3
# Measure SupraTentorial, SupraTentorialVol, Supratentorial volume, 939646.861571, mm^3
# Measure IntraCranialVol, ICV, Intracranial Volume, 1495162.656130, mm^3
```

Details:
https://surfer.nmr.mgh.harvard.edu/fswiki/MorphometryStats
http://surfer.nmr.mgh.harvard.edu/fswiki/eTIV

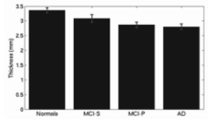
CORTICAL AUTOMATIC PARCELLATION (aparc)

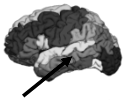
Thickness and Area ROI Studies



Entorhinal Cortex

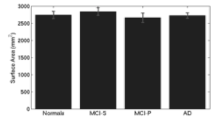
Thickness of Entorhinal Cortex





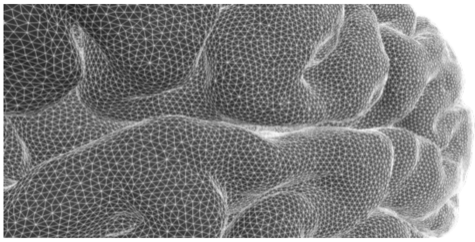
Middle Temporal Gyrus

Surface Area of MTG



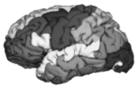
Gray matter volume also possible

Surface Mesh (zoom-in)

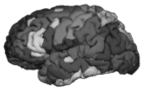


Parcellation/Annotation

- Surface ONLY
- Annotation format (*something.annot*)
- Each vertex has only one label/index
- Index List also found in color lookup table (LUT)
  - $FREESUFER_HOME/FreeSurferColorLUT.txt

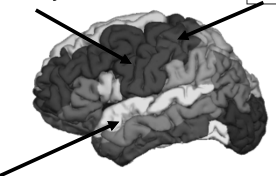


?h.aparc.annot



?h.aparc.a2009.annot

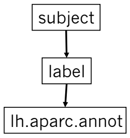
Automatic Surface Parcellation: Desikan/Killiany Atlas (35 ROI's)



Precentral Gyrus

Postcentral Gyrus

Superior Temporal Gyrus



subject

label

lh.aparc.annot

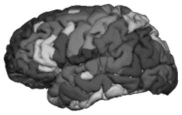
An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest, Desikan, R.S., F. Segonne, B. Fischl, B.T. Quinn, B.C. Dickerson, D. Blacker, R.L. Buckner, A.M. Dale, R.P. Maguire, B.T. Hyman, M.S. Albert, and R.J. Killiany, (2006). NeuroImage 31(3): 968-80.

Desikan/Killiany Atlas

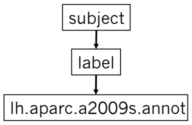
- 40 Subjects
- 14 Male, 26 Female
- Ages 18-87
- 30 Non-demented
- 10 Demented
- Siemens 1.5T Vision (Wash U)

An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest, Desikan, R.S., F. Segonne, B. Fischl, B.T. Quinn, B.C. Dickerson, D. Blacker, R.L. Buckner, A.M. Dale, R.P. Maguire, B.T. Hyman, M.S. Albert, and R.J. Killiany, (2006). NeuroImage 31(3): 968-80.

Automatic Surface Parcellation: Destrieux Atlas



- 58 Parcellation Units
- 12 Subjects



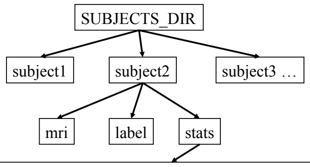
subject

label

lh.aparc.a2009s.annot

Automatically Parcellating the Human Cerebral Cortex, Fischl, B., A. van der Kouwe, C. Destrieux, E. Halgren, F. Segonne, D. Salat, E. Busa, L. Seidman, J. Goldstein, D. Kennedy, V. Caviness, N. Makris, B. Rosen, and A.M. Dale, (2004). Cerebral Cortex, 14:11-22.

FreeSurfer Stats Outputs



SUBJECTS_DIR

subject1 subject2 subject3 …

mri label stats

lh.aparc.stats	– left hemi Desikan/Killiany surface stats
rh.aparc.stats	– right hemi Desikan/Killiany surface stats
lh.aparc.a2009.stats	– left hemi Destrieux
rh.aparc.a2009.stats	– right hemi Destrieux

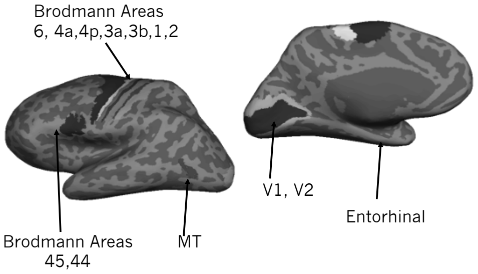
created by mris_anatomical_stats

Parcellation Stats File

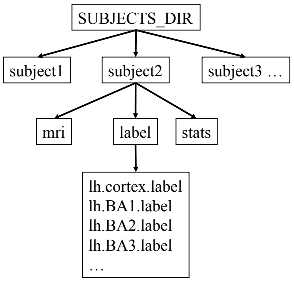
```
StructName             NumVert SurfArea GrayVol ThickAvg ThickStd MeanCurv GausCurv FoldInd CurvInd

bankssts            1157    811     1992    2.303    0.567    0.117    0.031       10     1.6
caudalanteriorcingulate    779     543     1908     3.472    0.676    0.185    0.064       26     1.8
caudalmiddlefrontal        3145    2137    5443     2.311    0.593    0.132    0.041       35     5.3
cuneus              1809   1195     2286    1.672    0.411    0.162    0.067       34     4.6
entorhinal          436     265     1269    2.871    0.881    0.119    0.037        5     0.6
fusiform            3307    2126    5161    2.109    0.689    0.144    0.064       71     8.7
inferiorparietal    5184    3514    8343    2.136    0.552    0.146    0.055       82    11.5
inferiortemporal    3746    2610    8752    2.683    0.748    0.178    0.132      140    18.0
```

StructName:	Name of structure/ROI
NumVert:	Number of vertices in ROI
SurfArea:	Surface area in mm2
GrayVol:	Volume of gray matter (surface-based)
ThickAvg/ThickStd:	Average and stddev of thickness in ROI
MeanCurv:	Mean curvature
GausCurv:	Mean Gaussian curvature
FoldInd:	Folding index
CurvInd:	Curvature index

Other ROIs (ex vivo)



Example Label Files



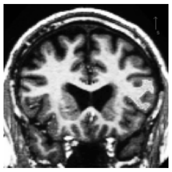
SUBJECTS_DIR

subject1 subject2 subject3 …

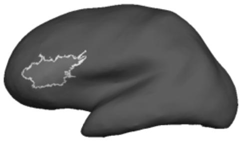
mri label stats

lh.cortex.label
lh.BA1.label
lh.BA2.label
lh.BA3.label
…

Label File



In Volume



On Surface

- Easy to draw
- Use ‘Select Voxels’ Tool in tkmedit
- Or use FreeView
- Simple text format

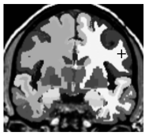
Creating Label Files

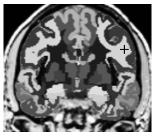
- Drawing tools:
  - tkmedit, freeview
  - tksurfer
  - QDEC
- Deriving from other data

mris_annotation2label:	cortical parcellation broken into units
mri_volcluster:	a volume made into a cluster
mri_surfcluster:	a surface made into a cluster
mri_vol2label:	a volume/segmentation made into a label
mri_label2label:	label from one space mapped to another

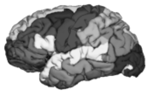
WHITE MATTER SEGMENTATION (wmparc)

Gyral White Matter Segmentation

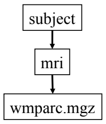




wmparc.mgz



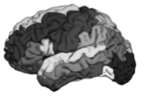
Nearest Cortical Label
to point in White Matter



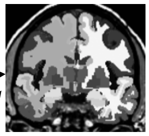
subject
mri
wmparc.mgz

Salat, et al., Age-associated alterations in cortical gray and white matter signal intensity and gray to white matter contrast. *Neuroimage* **2009,** 48, (1), 21-8.

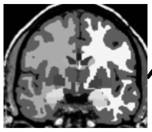
Merged Cortical + Subcortical



aparc

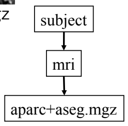


aparc+aseg.mgz



aseg.mgz

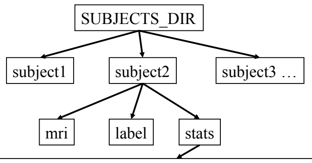
No new information
For visualization only



subject
mri
aparc+aseg.mgz

ANALYSIS of STATS

FreeSurfer Stats Outputs



SUBJECTS_DIR

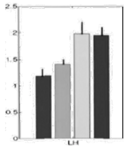
subject1
subject2
subject3 …

mri
label
stats

aseg.stats	– subcortical volumetric stats
wmparc.stats	– white matter segmentation volumetric stats
lh.aparc.stats	– left hemi Desikan/Killiany surface stats
rh.aparc.stats	– right hemi Desikan/Killiany surface stats
lh.aparc.a2009.stats	– left hemi Destrieux
rh.aparc.a2009.stats	– right Destrieux

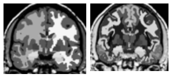
Extract table of subcortical volumes of all structures for all subjects

```
asegstats2table
  --subjects 001 002 003 004 005
  --meas volume
  --stats aseg.stats
  --tablefile  aseg.table.txt
```

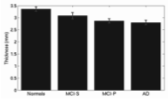


Applies to wmparc.stats too:
(--stats wmparc.stats)

Output is a simple ASCII text file



Extract table of average thickness of all cortical structures for all subjects

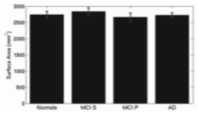


```
aparcstats2table
   --subjects 001 002 003
   --hemi lh
   --meas thickness
   --parc aparc
   --tablefile  aparc_lh_thickness_table.txt
```

Desikan/Killiany Atlas: --parc aparc

Destrieux Atlas: --parc aparc.a2009s

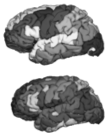
Extract table of surface area of all cortical structures for all subjects



```
aparcstats2table
   --subjects 001 002 003
   --hemi lh
   --meas area
   --parc=aparc
   --tablefile  aparc_lh_area_table.txt
```

Extract table of GM volume of <u>cortical</u> structures for all subjects

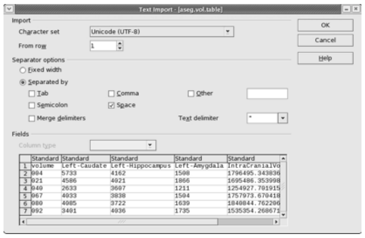
```
aparcstats2table
   --subjects 001 002 003
   --hemi lh
   --meas volume
   --parc=aparc
   --tablefile  aparc_lh_volume_table.txt
```



Note that the volume of cortical ROIs is extracted with aparcstats2table whereas the volume of subcortical structures is extracted with asegstats2table.

Importing Table Files

- SPSS, oocalc, matlab, R
- Choose: Delimited by spaces



	Standard	Standard	Standard	Standard	Standard
1	volume	Left-Caudate	Left-Hippocampus	Left-Amygdala	IntraCranialVo
2	004	5733	4162	1508	1796495.343836
3	021	4586	4021	1866	1695486.353998
4	040	2633	3607	1211	1254927.701915
5	067	4033	3838	1504	1757973.670418
6	080	4085	3722	1639	1840844.762206
7	092	3401	4036	1735	1535354.268671

GLM Analysis on Stats Files

- mri_glmfit (used for image-based group analysis)
- Use "--table table.txt" instead of "--y" to specify the input
- Eg, "mri_glmfit --table aparc_lh_vol_stats.txt …"
- The rest of the command-line is the same as you would use for a group study (e.g., FSGD file and contrasts).
- Output is text file sig.table.dat that lists the significances (-log10(p)) for each ROI and contrast.

Summary

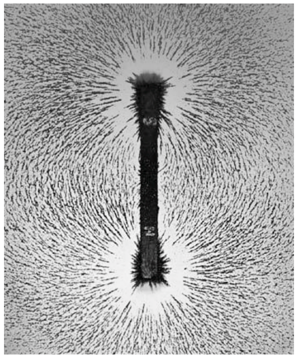
- ROIs are individualized
- Subcortical and WM ROIs (Volume)
- Surface ROIs (Volume, Area, Thickness)
- http://freesurfer.net/fswiki/MorphometryStats
- Segmentation vs. Annotation vs. Label File
- Extract to table (asegstats2table, aparcstats2table)
- Now we can do Multimodal Applications

Tutorial

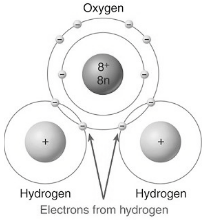
- Load and Inspect:
  - aparc+aseg.mgz
  - aparc.annot
  - FreeSurferColorLUT.txt
- View Individual Stats Files
- Group Table
  - Create
  - Load into spreadsheet

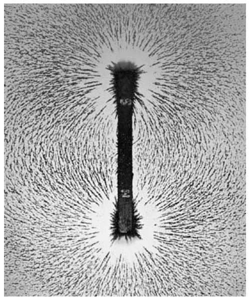
A Non-Physicist's Intro to MRI

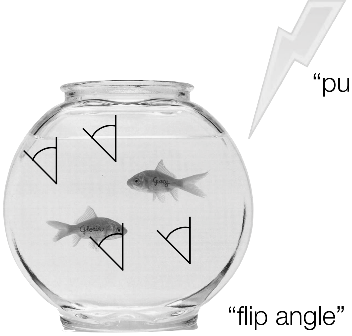
Dylan Tisdall



A human head

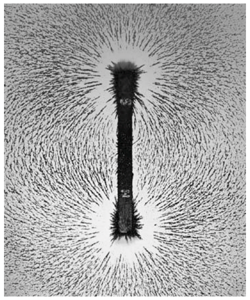




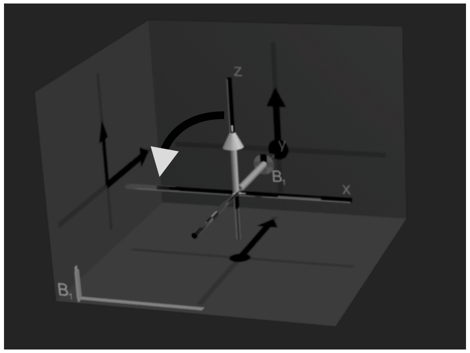


main
magnetic
field

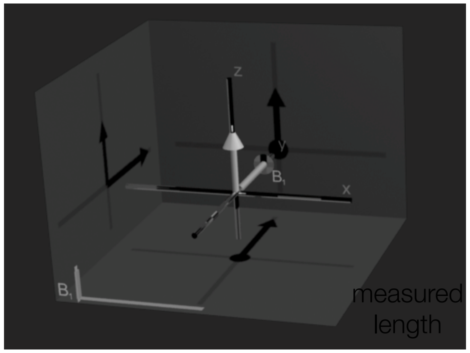
"flip angle"



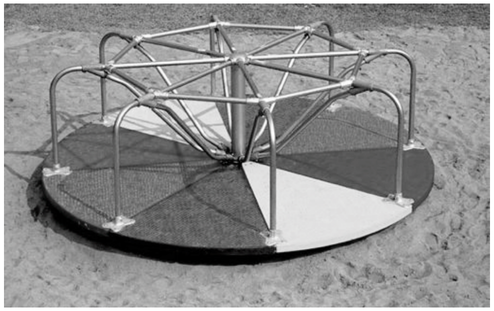
precession



The **rate of precession** changes **linearly** with the strength of the **magnetic field**

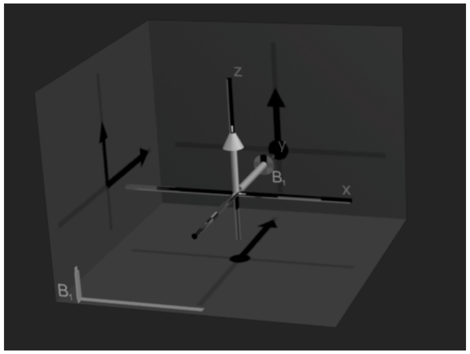


“rotating frame of reference”

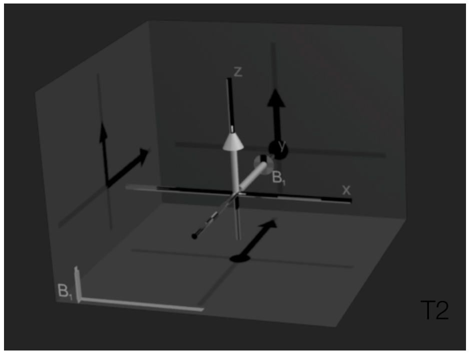


relaxation

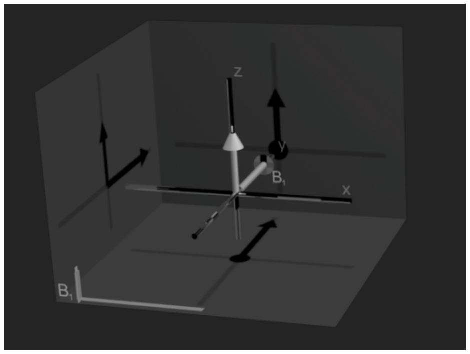
T2 is dephasing



dephasing looks like “less signal”



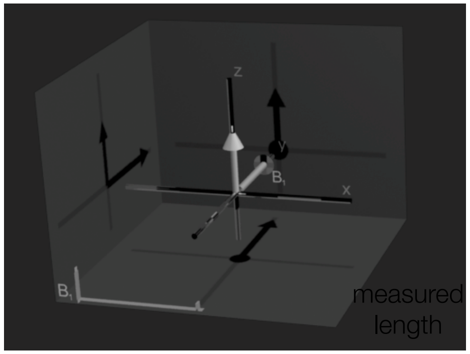
T1 and T2 relaxation



main
magnetic
field

The fish
are what
make it
interesting....

inversion recovery



Using **inversion recovery** we can **weight** our measurements for tissues with **specific T1**

How do we get
spatial information?

---

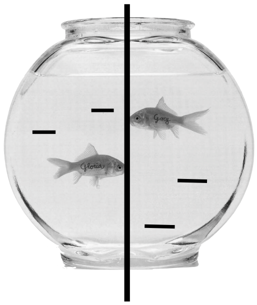
what do we measure?

main
magnetic
field

add up the red lines

---

two voxels (left and right)

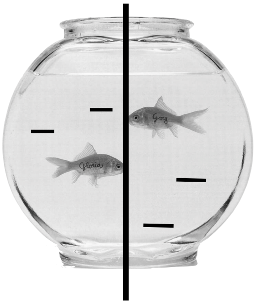


main
magnetic
field

take one measurement (sum)

---

two voxels (left and right)

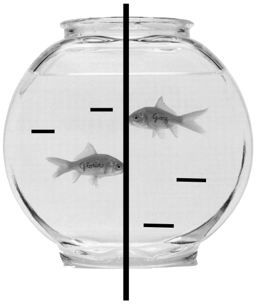


main
magnetic
field

apply a different magnetic field to each half

---

gradient

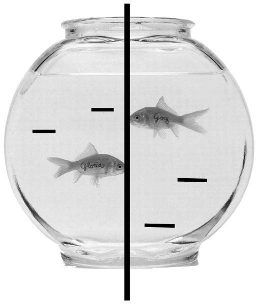


main
magnetic
field

apply a different magnetic field to each half

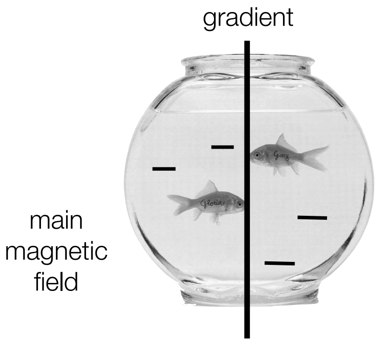
---

gradient



main
magnetic
field

rate of precession is different in each voxel

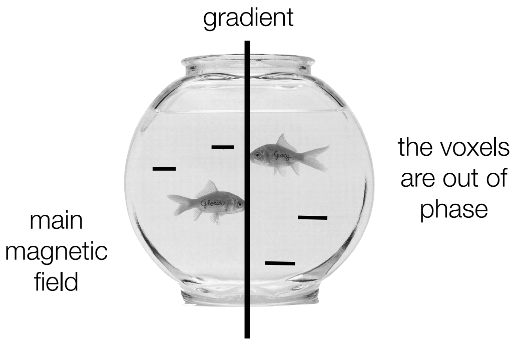


rate of precession is different in each voxel

1st measurement: left + right

2nd measurement: left - right

add them: 2 x left

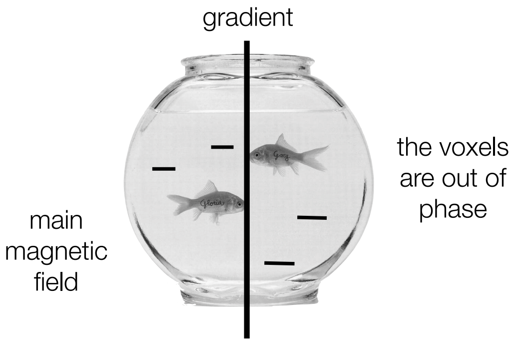


rate of precession is different in each voxel

1st measurement: left + right

2nd measurement: left - right

subtract them: 2 x right



take second measurement (sum)

Real sequences sum together fractional amounts from all the voxels.

The fractions are changed using the x-, y-, or z-gradients.

The voxels are “unmixed” from all the measurements using an Inverse Fourier Transform.

A Pulse Sequence

“Prepare” (invert, flip)

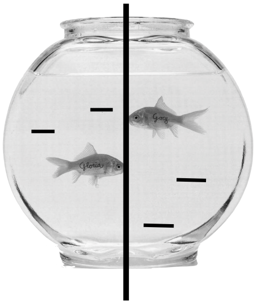
Localize (Gradients)

Measure

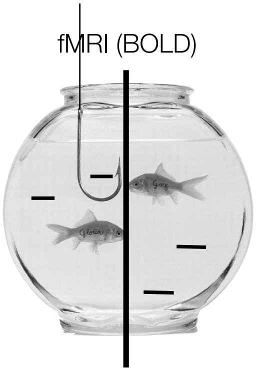
Relax

Go back to 1.

fMRI (BOLD)

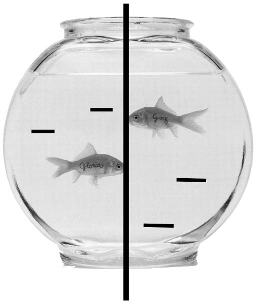


fMRI (BOLD)



this side dephases faster = less signal

fMRI (BOLD)



this side’s T2 returns to normal

MRI Acquisition Methods for Brain Morphometry

André J. W. van der Kouwe

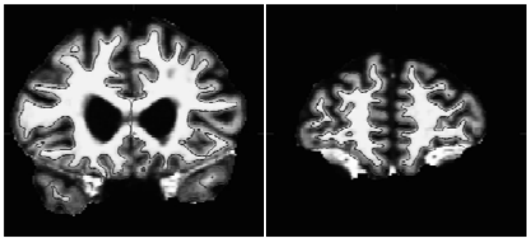
Athinoula A. Martinos Center, Massachusetts General Hospital

Avoiding Imaging Artifacts

Small mistakes in the choice of imaging protocol at the beginning of a study can result in a large amount of manual intervention work later on.

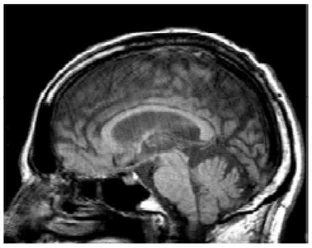
Examples of Artifacts

Chemical shift artifact



Examples of Artifacts

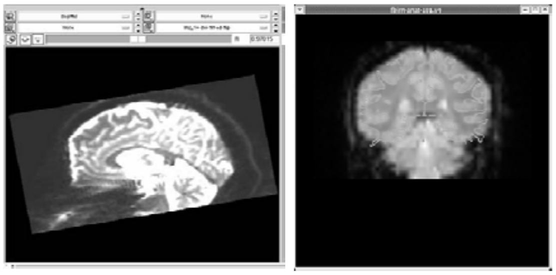
Motion artifact



INTRuST (Posttraumatic Stress Disorder and Traumatic Brain Injury Clinical Consortium) NLC (Neuroimaging Leadership Core): Shenton, Kikinis, Rosen (PIs), Helmer, van der Kouwe, Kubicki, Pasternak (http://intrust.spl.harvard.edu)

Examples of Artifacts

Intrinsic susceptibility artifact (EPI images)



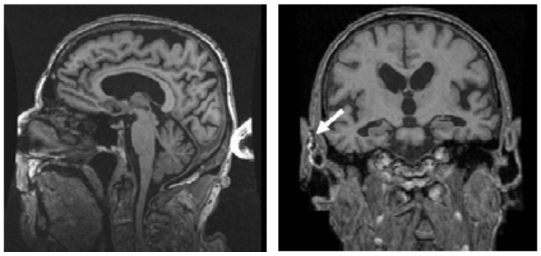
Examples of Artifacts

Susceptibility artifact from metal

INTRuST (Posttraumatic Stress Disorder and Traumatic Brain Injury Clinical Consortium) NLC (Neuroimaging Leadership Core): Shenton, Kikinis, Rosen (PIs), Helmer, van der Kouwe, Kubicki, Pasternak (http://intrust.spl.harvard.edu)

Examples of Artifacts

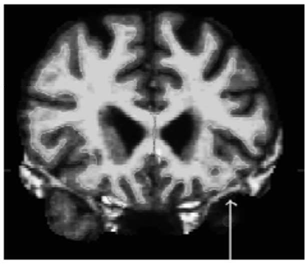
Wrap in phase encoding direction (3D has two PE directions)



INTRuST (Posttraumatic Stress Disorder and Traumatic Brain Injury Clinical Consortium) NLC (Neuroimaging Leadership Core): Shenton, Kikinis, Rosen (PIs), Helmer, van der Kouwe, Kubicki, Pasternak (http://intrust.spl.harvard.edu)

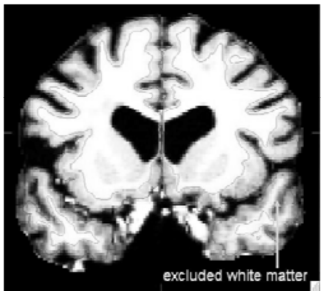
Examples of Artifacts

Dura adjacent to cortex



Examples of Artifacts

Poor contrast



MRI Acquisition Methods for Brain Morphometry

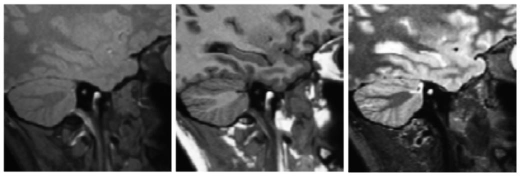
1. Contrasts: Bandwidth matched morphometry
   (PD, T1, T2 and T2*)
2. Artifacts: Distortions
   (B0 and gradient distortions)
3. Positioning: AutoAlign and motion correction

Contrasts: Bandwidth matched morphometry
(PD, T1, T2 and T2*)
Artifacts: Distortions
(B0 and gradient distortions)

Contrasts: PD, T1, T2 and T2* weighting

Which is best for brain morphometry/FreeSurfer?

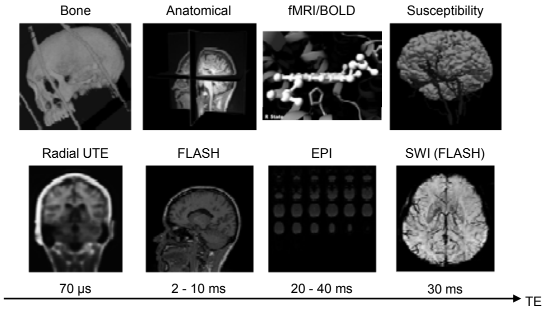
PD-weighting	+ T1-weighting	+ T2-weighting
(proton/spin density)	(gray/white contrast)	(bright CSF/tumor)



FLASH 5° FLASH 30° T2-SPACE

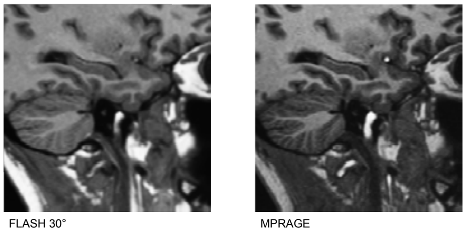
Contrasts: PD, T1, T2 and T2* weighting

T2*-weighting (bone/dark blood/blood oxygenation/susceptibility)



Contrasts: PD, T1, T2 and T2* weighting

Which is best for brain morphometry/FreeSurfer?



MPRAGE (FLASH with inversion) has the best contrast for FreeSurfer because:

- MPRAGE parameters chosen for “optimal” gray/white/CSF contrast
- FreeSurfer statistics (priors) based on MPRAGE

Recommended protocol: bandwidth matched

On the Martinos Center scanners under MGH → Morphometry:

Localizer		0:13
AAScout		0:46

For cortical thickness (MEMPRAGE):

tfl_mgh_me_4echoes_iPAT2	1 x 1 x 1 mm^3	6:03

For segmentation and PD/T1 estimation (MEFLASH):

gre_mgh_me_5deg_iPAT2	1 x 1 x 1 mm^3	8:28
gre_mgh_me_30deg_iPAT2	1 x 1 x 1 mm^3	8:28

For T2 contrast (lesion detection):

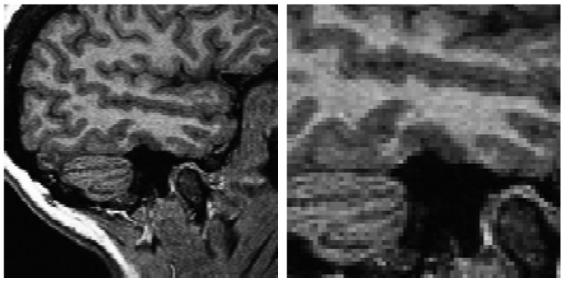
T2_SPACE_iPAT2	1 x 1 x 1 mm^3	4:43

Bandwidths are matched and iPAT/multichannel coils reduce time

Detailed recommended protocols at http://www.nmr.mgh.harvard.edu/~andre

Why multi-echo bandwidth matched?

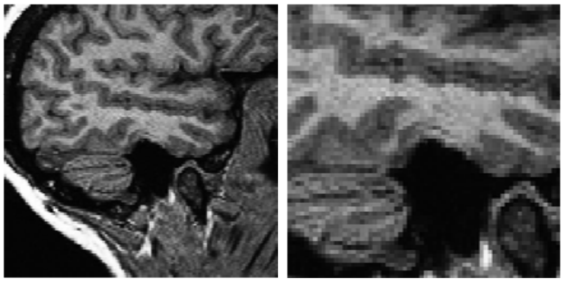
Geometric distortion with gradient echo sequences is proportional to ∆B0, inversely proportional to bandwidth and follows readout direction



MPRAGE with positive readout direction, BW 195 Hz/px (1 pixel shift for each 195 Hz error in B0)

Why multi-echo bandwidth matched?

Geometric distortion with gradient echo sequences is proportional to ∆B0, inversely proportional to bandwidth and follows readout direction



MPRAGE with negative readout direction, BW 195 Hz/px (-1 pixel shift for each 195 Hz error in B0)

Why multi-echo bandwidth matched?

High bandwidth results in:

- smaller B0 (susceptibility) related geometric distortions
- but lower SNR

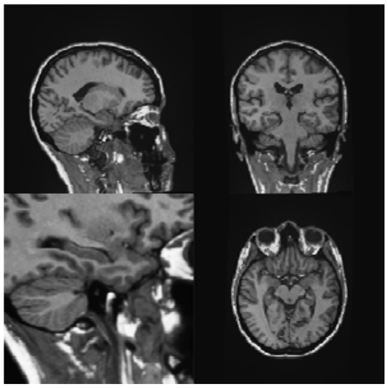
With multiecho sequences:

- individual echoes have high bandwidth/low SNR
- but echoes are combined to recover SNR with low distortion

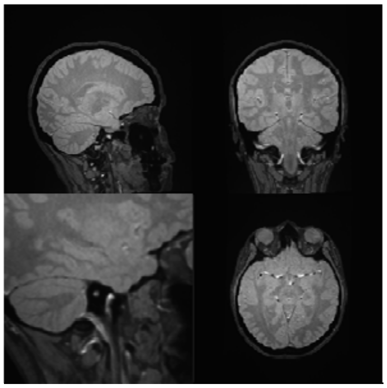
MEMPRAGE, MEFLASH and T2-SPACE can be bandwidth-matched:

- edges of structures align across contrasts

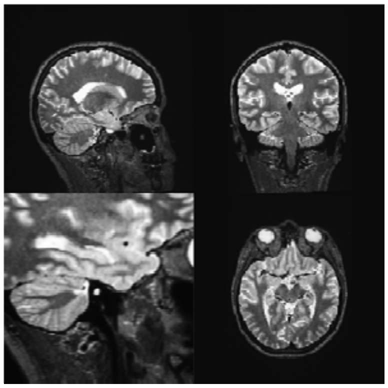
BW matched protocol: MEF 30° (mean)



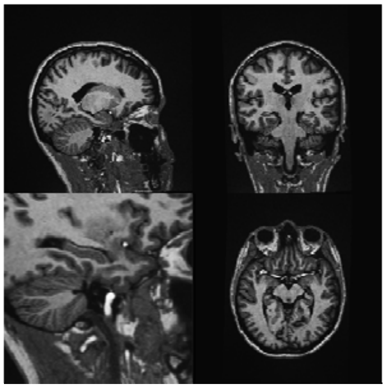
BW matched protocol: MEF 5° (mean)



BW matched protocol: T2-SPACE

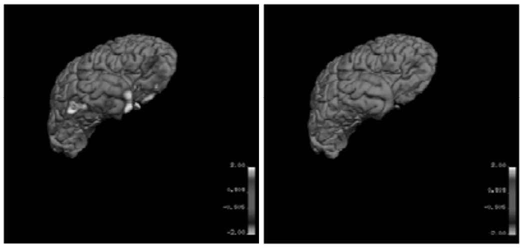


BW matched protocol: MEMPRAGE (RMS)



What areas of the cortical surface do B0 distortions affect the most?

Distances between surfaces measured with opposite readout directions (since both surfaces move, cortical thickness changes are much smaller)



MPRAGE (+) vs
MPRAGE (-)

MEMPRAGE (+-+-) vs
MEMPRAGE (-+-+)

Benner, Salat, MGH

Why collect FLASH at different flip angles?

FLASH (spoiled gradient echo) sequence is versatile, simple and easily modeled:

$$S(\alpha,P) = P\sin\alpha\left(\frac{1-e^{-TR/T_1}}{1-e^{-TR/T_1}\cos\alpha}\right)e^{-TE/T_2^*}$$

Effective T1 and PD (in arbitrary units) can be estimated at each voxel from two FLASH scans with differing flip angles using the FLASH steady-state equation (assume TE << T2*)

T2* can be estimated at each voxel from the signal decay across eight echoes of the multiecho FLASH scan (MEF)

The T1 and PD volumes can be used to synthesize a volume at any flip angle

Fischl, MGH; Dale, UCSD

T1 / PD / T2* fitting with FreeSurfer

FreeSurfer command to fit T1, PD and T2* from FLASH volumes:

```
mri_ms_fitparms [options] [vol_1] [vol_2] ... [output_dir]
```

For example:

```
mri_ms_fitparms -tr 20 -te 6 -fa 5 flash5.mgh -tr 20 -te 6 -fa 30
          flash30.mgh parameter_maps
```

(parameters_maps/ is destination directory)

FreeSurfer command to synthesize volume from T1 and PD:

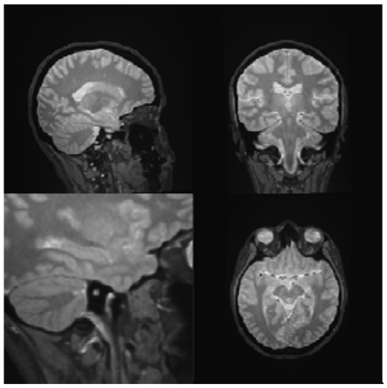
```
mri_synthesize [options] <TR> <alpha> <TE> <T1 vol>
          <PD vol> <output>
```

For example:

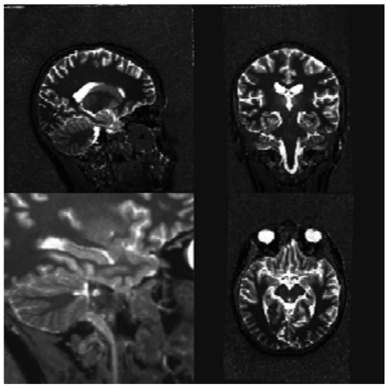
```
mri_synthesize  20  23  0  T1.mgz  T2.mgz  synth_23.mgz
```

Fischl, MGH; Dale, UCSD

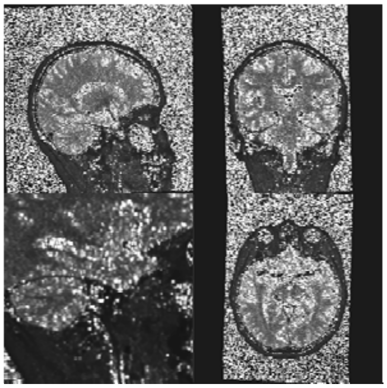
BW matched protocol: PD



BW matched protocol: T1

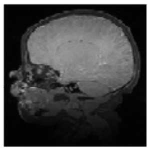


BW matched protocol: T2*

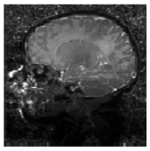


Why collect FLASH at different flip angles?

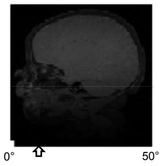
Volumes with arbitrary flip angles can be synthesized from PD and T1



PD volume



T1 volume



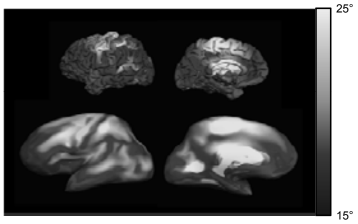
Synthetic volume

Ernst angle (flip angle α at which signal is maximized) can be calculated from T1 of tissue ($\cos \alpha = e^{-TR/T1}$) but this is not necessarily the angle of maximum contrast

Meintjes, UCT; Jacobson, WSU

Why collect FLASH at different flip angles?

Flip angle for best contrast varies with pairs of structures and within structures (e.g. gray/white contrast varies across cortex and with age)



Flip angle for best gray/white contrast (with TR 20 ms) displayed on cortex (young adult)

Salat, MGH

T2* in MEMPRAGE can be used to locate dura

In MPRAGE there is little contrast between dura and gray matter and dura is sometimes included within the pial surface

FreeSurfer can adjust the pial surface so that it excludes dura if MEMPRAGE volumes are available

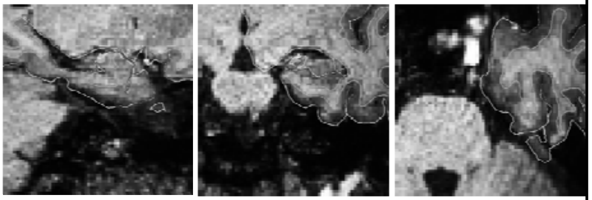
Echo 1

Fischl, Benner, MGH

T2* in MEMPRAGE can be used to locate dura

In MPRAGE there is little contrast between dura and gray matter and dura is sometimes included within the pial surface

FreeSurfer can adjust the pial surface so that it excludes dura if MEMPRAGE volumes are available

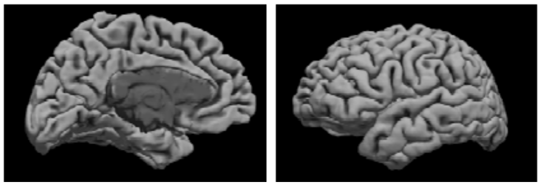


Echo 4

Fischl, Benner, MGH

T2* in MEMPRAGE can be used to locate dura

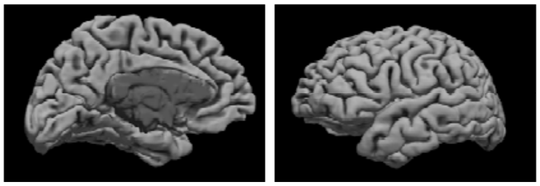
Surface including dura



Fischl, Benner, MGH

T2* in MEMPRAGE can be used to locate dura

Surface after removal of dura



Fischl, Benner, MGH

Dura correction with FreeSurfer

FreeSurfer command to correct dura:

```
mris_make_surfaces      –dura filename_%d.mgz
                        -${lastecho}
                        -aseg aseg.auto.mgz
                        -mgz
                        -sdir ${SUBJECTS_DIR}
                        -output _dura_1and${lastecho}
                        $({target} ${hemi}
```

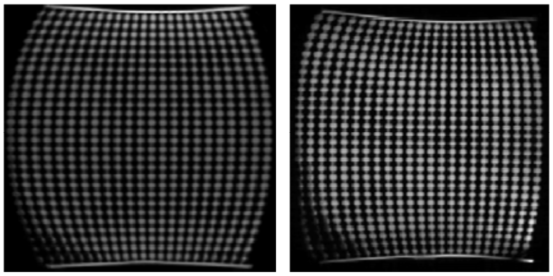
where filename_%d.mgz refers to the four separated echoes of the MEMPRAGE and lastecho = 4

Generates:

lh.pial_dura_1and4, rh.pial_dura_1and4,
lh.white_dura_1and4, rh.white_dura_1and4

Fischl, Benner, MGH

Gradient distortion: uncorrected

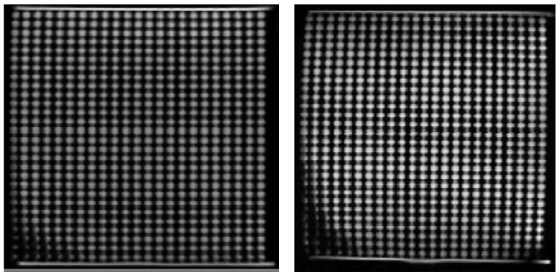


GE Whole-Body
CRM NVi/CVi

Siemens Whole-Body
Symphony/Sonata

Balasubramanian, BU/Tufts; Dale, UCSD

Gradient distortion: corrected



GE Whole-Body
CRM NVi/CVi

Siemens Whole-Body
Symphony/Sonata

Balasubramanian, BU/Tufts; Dale, UCSD

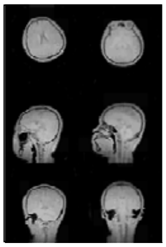
Positioning: AutoAlign and Motion Correction

Background: AutoAlign

Place subject in scanner and acquire AutoAlign localizer (44 s)

Scanner registers acquired brain to average statistical atlas (10 s)

Scan prescriptions for subsequent scans in session are prospectively positioned in standard orientation - therefore also aligned to scans from previous sessions



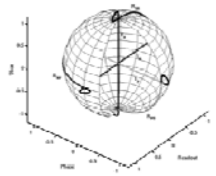
AutoAligned position

Actual position

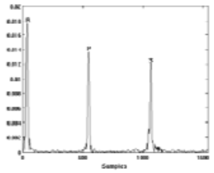
Chen, Gicquel, Cortechs Laboratories
Dale, UCSD

Motion correction: Cloverleaf navigators

Cloverleaf navigators are designed to enable a rigid body position estimate in a single readout of less than 5 ms



Cloverleaf k-space trajectory



Navigator signal magnitude

Dale, UCSD

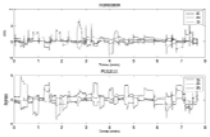
Motion correction: Cloverleaf navigators

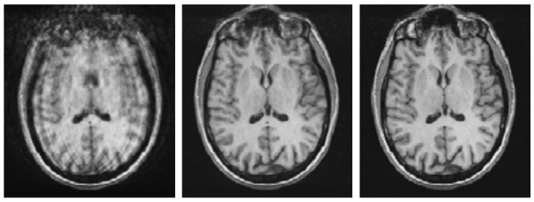
Cloverleaf navigators assess and correct for the position of an object in the scanner every TR of a modified FLASH scan (e.g. every 20 ms)

Wald, Dale, MGH

Human results

Cloverleaf navigator correction substantially improved image quality in volunteers performing deliberate head motions





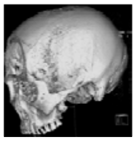
Average
No motion correction

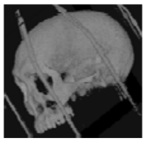
Average (equal weight)
Real-time motion corr.

Average (MSE weighted)
Real-time motion corr.

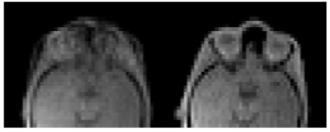
3D FLASH (TR=20 ms, TE=10 ms, 1.3 x 1 x 1.3 mm, Tacq=7:45, BW=160 Hz/pixel)

Motion correction: Radial imaging (UTE)


CT


MRI

3D radial imaging (UTE) may be used to image bone for attenuation correction in MR-PET. Motion during acquisition and subsequent position changes may invalidate the attenuation correction map. This method may be extended to fetal imaging.

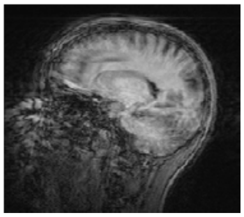


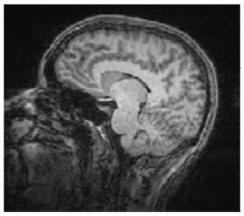
Motion during a 1 min 18 s radial 3D acquisition

Protocol: TR 2.39 ms, single ultrashort echo with TE 50 μs, BW 1002 Hz/px, flip angle 2°, FoV 256 mm, resolution 4^3 mm^3.
System: 3 T Siemens (Erlangen, Germany) Tim Trio, 32 channel head coil.

MPRAGE with EPI navigators

EPI navigators inserted every TR of MEMPRAGE capture a “snapshot” of subject’s head and allow real-time tracking/correction, also for T2-SPACE. This work will be presented on Friday.


No motion correction


Motion correction

Tisdall, MGH; Hess, UCT; Meintjes, UCT

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Michael Hamm
Keith Heberlein
Franz Hebrank
Aaron Hess
Oliver Hinds
Joseph Jacobson
Sandra Jacobson
John Kirsch
Ernesta Meintjes
Maria Mody
Erez Nevo
Josef Pfeuffer
Rudolph Pienaar
Allison Player
Jonathan Polimeni
David Salat
Nick Schmansky
Franz Schmitt
Ravi Seethamraju
Simon Sigalovsky
A. Gregory Sorensen
Krish Subramaniam
M. Dylan Tisdall
Lawrence Wald
Larry White
Paul Wighton

Motion-Compensated Neuroanatomical Imaging

Dylan Tisdall
April 2013

Motion-compensated MRI sequences allow you to image subjects ***even if they move***, without discarding scans and rescanning.

There are two basic types of motion-compensation:

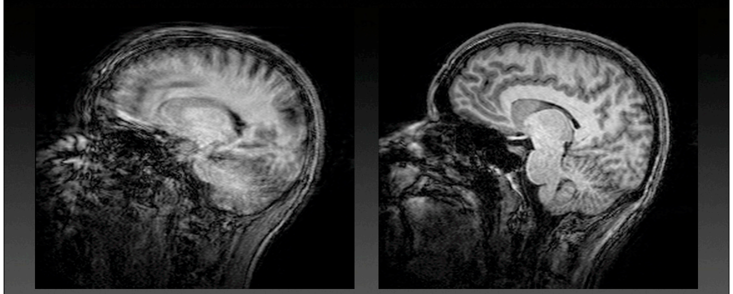
Retrospective

Post-process to estimate data that would have been measured if the subject hadn't moved.
Examples: PROPELLER, SNAILS

Prospective

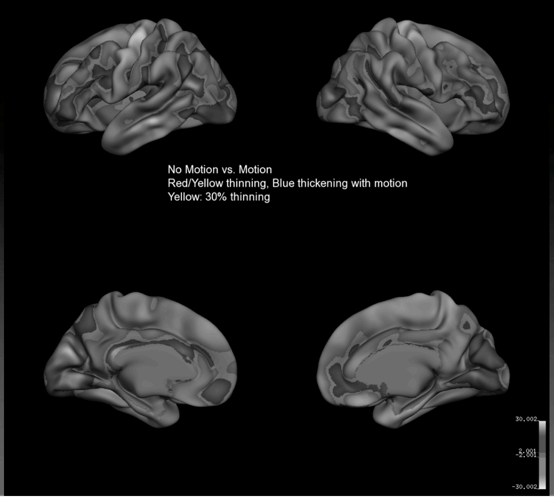
Track the subject and alter the acquisition "on-the-fly" to account for subject motion.
Examples: PACE, vNavs, PROMO

MPRAGE of subject prompted to change position every 45 seconds

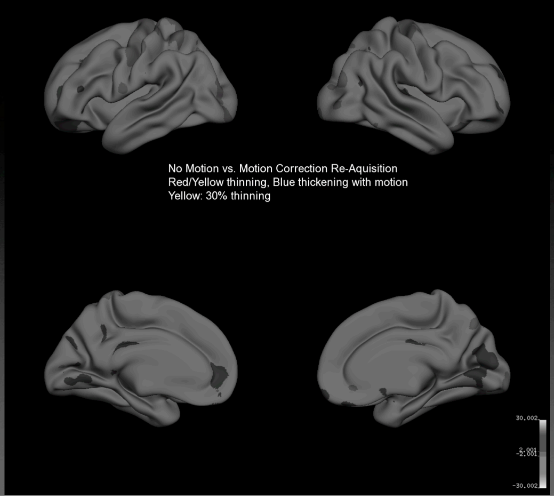


without prospective moco

with prospective moco



No Motion vs. Motion
Red/Yellow thinning, Blue thickening with motion
Yellow: 30% thinning



No Motion vs. Motion Correction Re-Aquisition
Red/Yellow thinning, Blue thickening with motion
Yellow: 30% thinning

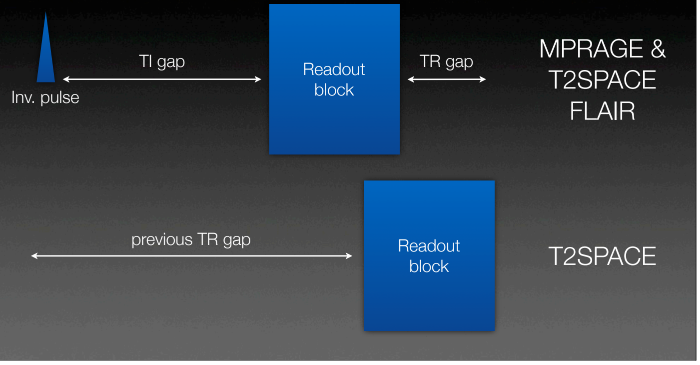
Who should use these sequences? Everyone!

- Our vNav sequences are available now on Siemens scanners (WIP 711).
- Other groups are developing similar techniques on GE scanners (e.g., PROMO).

Overview

- **Following the subject:**
  EPI-navigated prospective motion correction
- **More motion-resistance:**
  automatic retrospective reacqusition
- **Using FreeSurfer for validation:**
  longitudinal, cross-contrast analysis

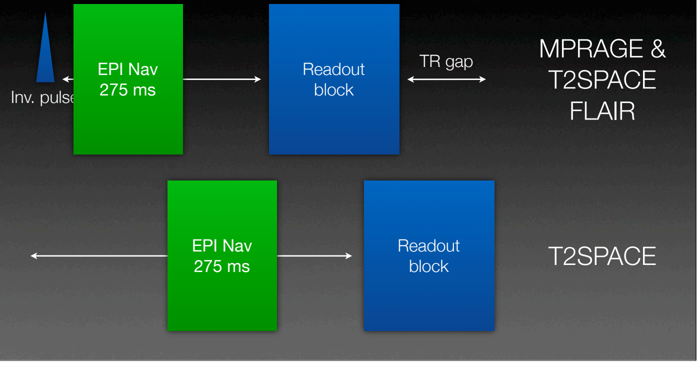
A single TR



Inv. pulse
TI gap
Readout block
TR gap
MPRAGE &
T2SPACE
FLAIR

previous TR gap
Readout block
T2SPACE

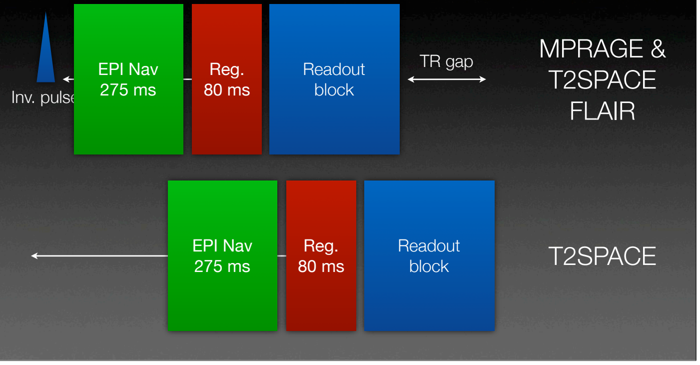
A single TR
+ EPI Navigator



Inv. pulse
EPI Nav
275 ms
Readout block
TR gap
MPRAGE &
T2SPACE
FLAIR

EPI Nav
275 ms
Readout block
T2SPACE

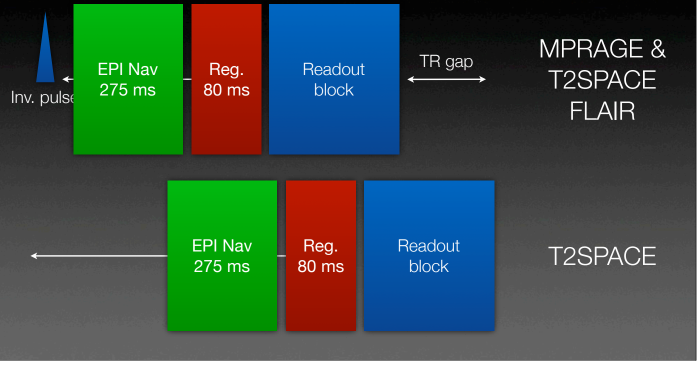
A single TR
+ EPI Navigator
+ Registration and Feedback



Inv. pulse
EPI Nav
275 ms
Reg.
80 ms
Readout block
TR gap
MPRAGE &
T2SPACE
FLAIR

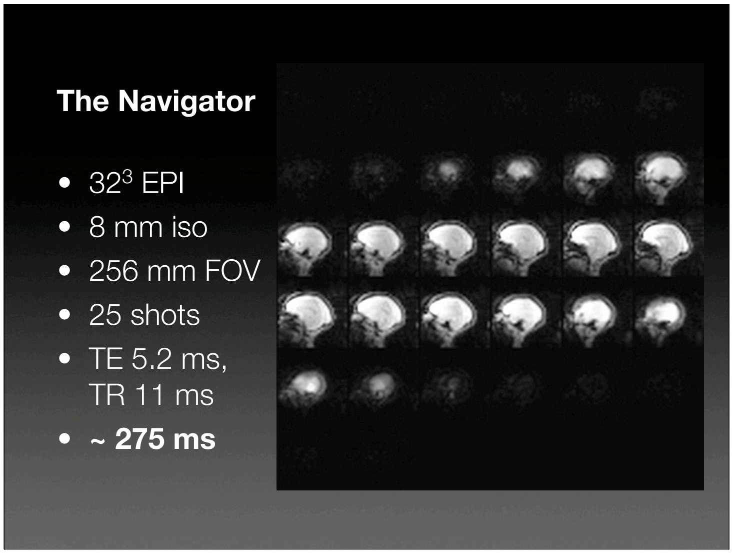
EPI Nav
275 ms
Reg.
80 ms
Readout block
T2SPACE

A single TR
+ EPI Navigator
+ Registration and Feedback
= updated imaging coordinates



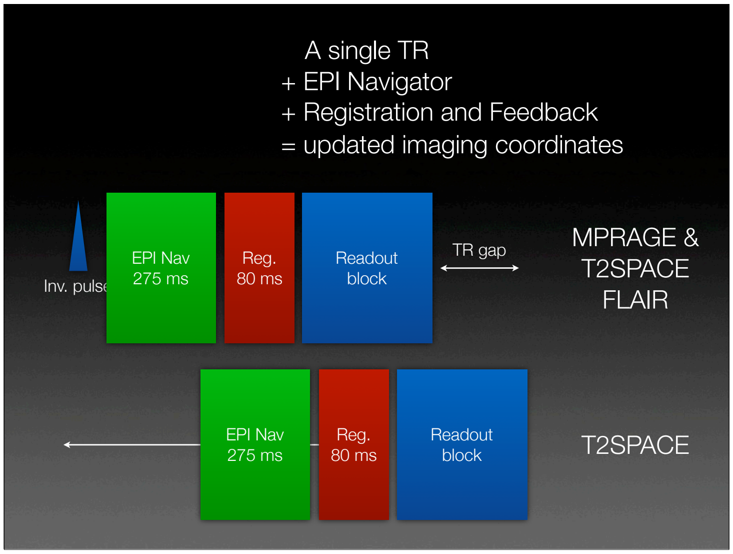
Inv. pulse
EPI Nav
275 ms
Reg.
80 ms
Readout block
TR gap
MPRAGE &
T2SPACE
FLAIR

EPI Nav
275 ms
Reg.
80 ms
Readout block
T2SPACE

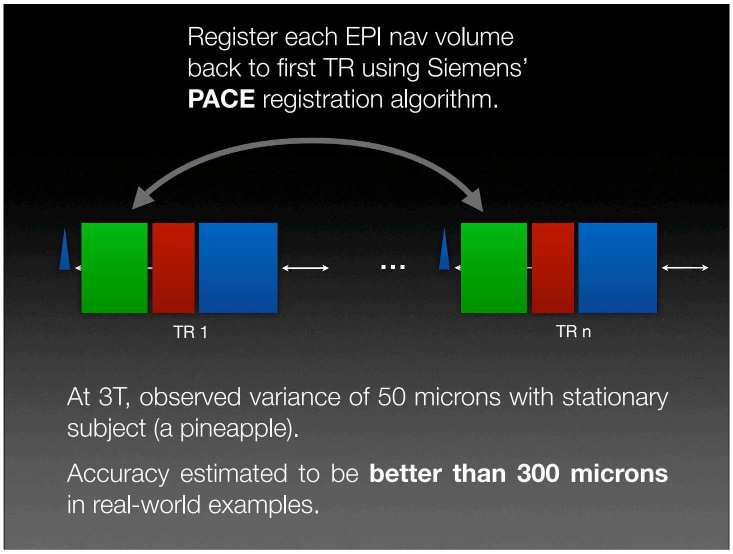


The Navigator

- 32^3 EPI
- 8 mm iso
- 256 mm FOV
- 25 shots
- TE 5.2 ms, TR 11 ms
- **~ 275 ms**



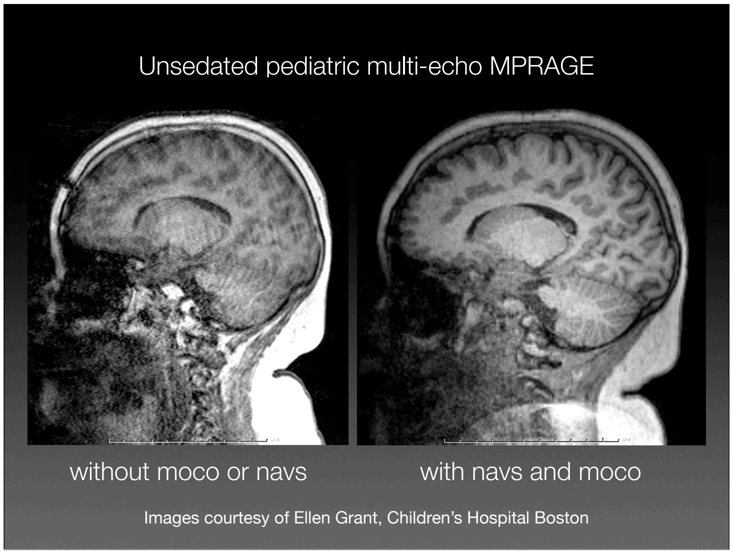
A single TR
+ EPI Navigator
+ Registration and Feedback
= updated imaging coordinates



Register each EPI nav volume back to first TR using Siemens' **PACE** registration algorithm.

At 3T, observed variance of 50 microns with stationary subject (a pineapple).

Accuracy estimated to be **better than 300 microns** in real-world examples.



Unsedated pediatric multi-echo MPRAGE

without moco or navs

with navs and moco

Images courtesy of Ellen Grant, Children's Hospital Boston

Overview

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  EPI-navigated prospective motion correction
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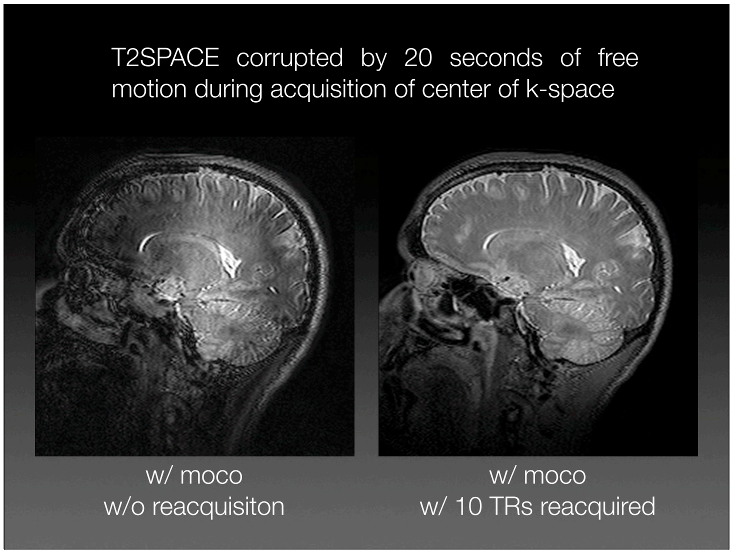
  automatic retrospective reacqusition
- **Using FreeSurfer for validation:**
  longitudinal, cross-contrast analysis

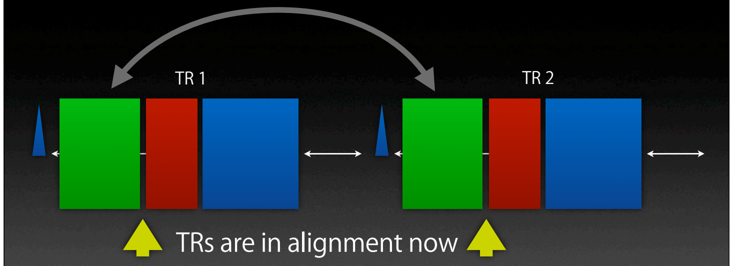


T2SPACE corrupted by 20 seconds of free motion during acquisition of center of k-space

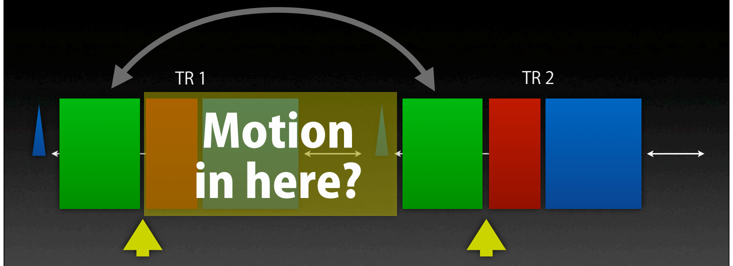
w/ moco
w/o reacquisiton

w/ moco
w/ 10 TRs reacquired

Register each EPI nav volume
back to first TR using Siemens'
PACE registration algorithm.

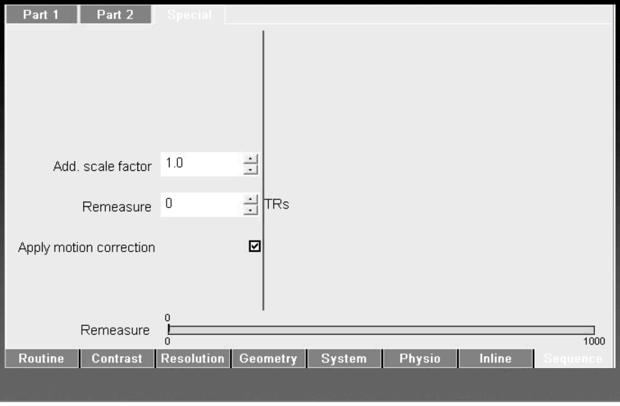


TRs are in alignment now



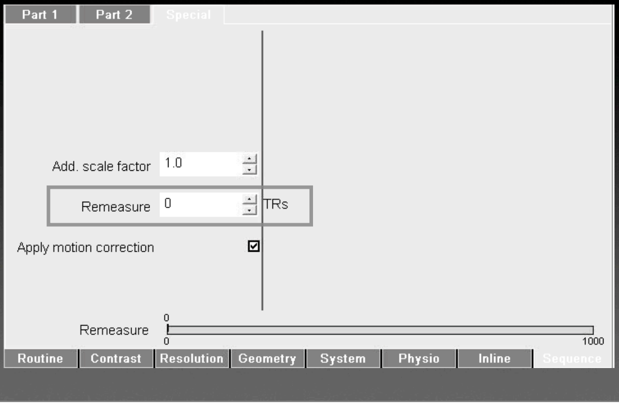
Motion in here?

Users configure the number of TRs to reacquire as part of their protocol.

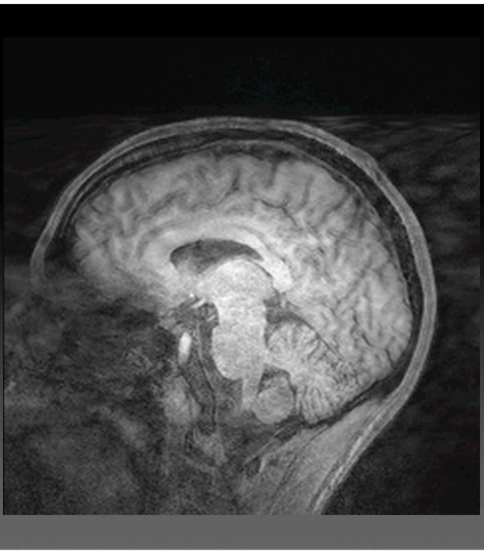


Add. scale factor 1.0
Remeasure 0 TRs
Apply motion correction ☑
Remeasure 0 (0–1000)

Users configure the number of TRs to reacquire as part of their protocol.



Add. scale factor 1.0
Remeasure 0 TRs
Apply motion correction ☑
Remeasure 0 (0–1000)



Overview

- **Following the subject:**
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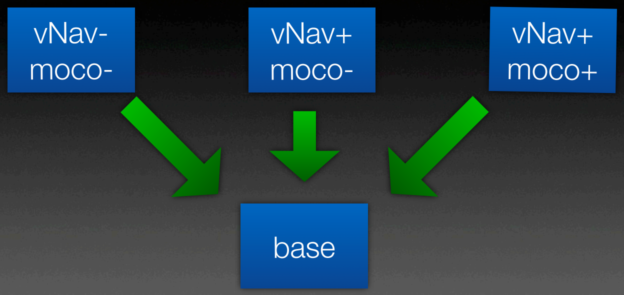
- **More motion-resistance:**
  automatic retrospective reacqusition
- **Using FreeSurfer for validation:**
  longitudinal, cross-contrast analysis

Three non-standard FreeSurfer uses

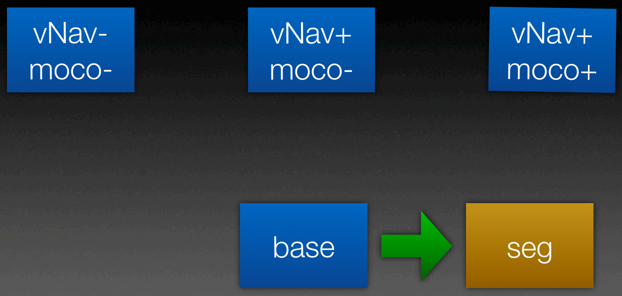
1. “Longitudinal” analysis of same-subject, same-day, motion-free T1 scans without navigators, with navigators but without motion-correction, and with navigators and motion-correction.
2. Registration of same-subject, same-day, with-motion T1 scans to a fully segmented same-subject, same-day, without-motion T1 scan.
3. Cross-contrast registration of same-subject, same-day, with- and without-motion T2 scans to a fully segmented same-subject, same day without motion T1 scan.

“Longitudinal” analysis of same-subject, same-day, motion-free T1 scans without navigators, with navigators but without motion-correction, and with navigators and motion-correction.



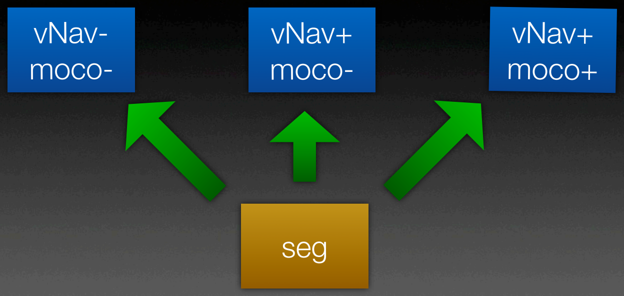
longitudinal stream

“Longitudinal” analysis of same-subject, same-day, motion-free T1 scans without navigators, with navigators but without motion-correction, and with navigators and motion-correction.



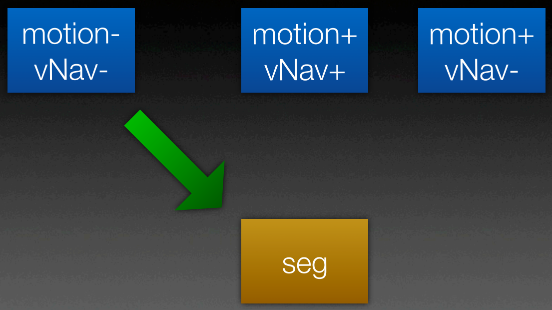
longitudinal stream

“Longitudinal” analysis of same-subject, same-day, motion-free T1 scans without navigators, with navigators but without motion-correction, and with navigators and motion-correction.



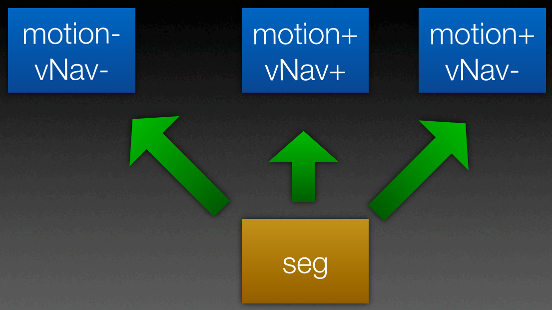
now we have voxel-wise equivalence

Registration of same-subject, same-day, with-motion T1 scans to a fully segmented same-subject, same-day, without-motion T1 scan.



cross-sectional stream

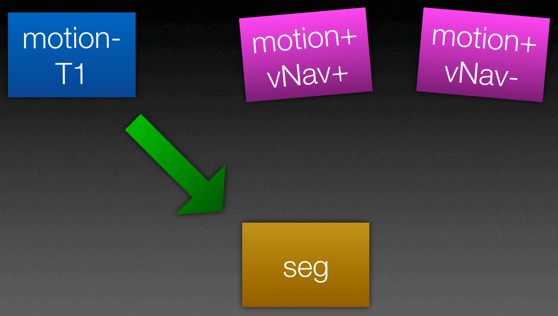
Registration of same-subject, same-day, with-motion T1 scans to a fully segmented same-subject, same-day, without-motion T1 scan.



now we have voxel-wise equivalence

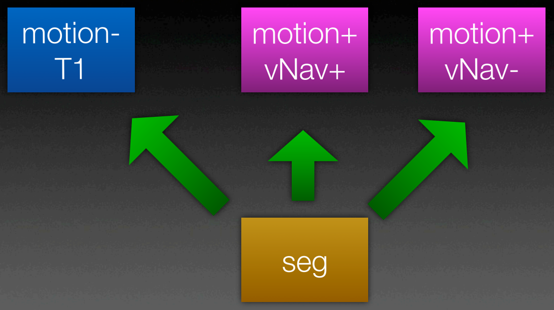
We can use mri_robust_register to **extrapolate a segmentation** to a subsequent acquisition.

Cross-contrast registration of same-subject, same-day, with- and without-motion T2 scans to a fully segmented same-subject, same day without motion T1 scan.



cross-sectional stream

Cross-contrast registration of same-subject, same-day, with- and without-motion T2 scans to a fully segmented same-subject, same day without motion T1 scan.



now we have voxel-wise equivalence

We can use bbregister to **extrapolate a segmentation** to a subsequent acquisition with a different contrast.

Acknowledgements:

- Aaron Hess
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- Martin Reuter
- Himanshu Bhat
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MGH/HST Athinoula A. Martinos
Center for Biomedical Imaging

MASSACHUSETTS GENERAL HOSPITAL
HST Harvard-MIT Health Sciences & Technology

Surface-based Group Analysis in FreeSurfer

Outline

- Objectives & Example
- GLM Theory & Linear Algebra Review
- Command-line Stream
  - Assemble Data
  - Design/Contrast
  - Analyze
  - Visualize

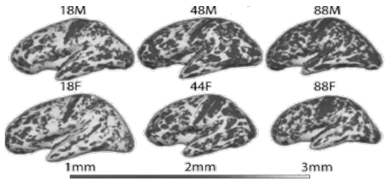
Group Analysis Objective

- To create a model that can describe patterns of interactions and associations
- The **parameters** of the model provide measures of the strength of associations
- A General Linear Model (GLM) focuses on *estimating the parameters of the model* such that they can be applied to new data sets to create reasonable inferences.

Types of Questions

- Does a specific variable have a significant association with an outcome?
- If we control for the effects of a second variable, is the association still significant?
- Is there a group difference in outcome?
- Does a specific variable affect individual outcome differently between groups of individuals?

Aging Exploratory Analysis

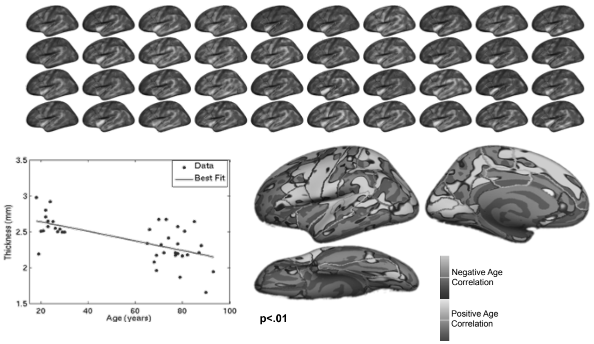


In which areas does thickness
Change with age?

Cortical Thickness vs Aging
Salat et al, 2004, Cerebral Cortex

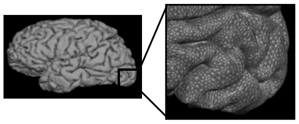
Aging Thickness Study

N=40 (all in fsaverage space)



Surface-based Measures

- Morphometric (e.g., thickness)
- Functional
- PET
- MEG/EEG
- Diffusion (?) sampled just under the surface



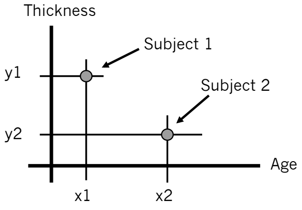
The General Linear Model (GLM)

GLM Theory

Is Thickness correlated with Age?

Dependent Variable, Measurement

Thickness
IQ, Height, Weight, etc.



Of course, you would need more then two subjects ...

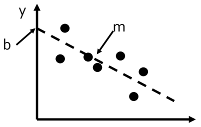
Independent Variable

Linear Algebra Review (stay calm...)

Dependent variable (outcome) → $y = mx + b$ ← Intercept

Slope

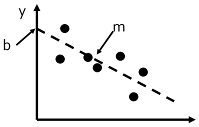
Independent variable



Linear Algebra Review (stay calm...)

We can put this in matrix format:

$y = mx + b$



$$\begin{pmatrix} y1 \\ y2 \\ y3 \\ y4 \end{pmatrix} = \underbrace{\begin{pmatrix} 1 & x1 \\ 1 & x2 \\ 1 & x3 \\ 1 & x4 \end{pmatrix}}_{\textbf{Design Matrix}} * \underbrace{\begin{pmatrix} b \\ m \end{pmatrix}}_{\textbf{Regression Coefficients (parameters)}}$$

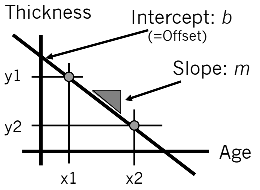
·One row per data point
·Add column of 1's for the offset term (*b*)
·One set of parameters

Matrix Multiplication

$$\begin{pmatrix} y1 \\ y2 \\ y3 \\ y4 \end{pmatrix} = \begin{pmatrix} 1 & x1 \\ 1 & x2 \\ 1 & x3 \\ 1 & x4 \end{pmatrix} * \begin{pmatrix} b \\ m \end{pmatrix}$$

$$\left.\begin{aligned} y1 &= 1*b + x1*m \\ y2 &= 1*b + x2*m \\ y3 &= 1*b + x3*m \\ y4 &= 1*b + x4*m \end{aligned}\right\} \text{System of Linear Equations}$$

Linear Model



X = Design Matrix
b = Regression Coefficients
= Parameter estimates
= “betas”
= beta.mgh (mri_glmfit output)

System of Linear Equations
y1 = 1**b* + x1**m*
y2 = 1**b* + x2**m*

Matrix Formulation

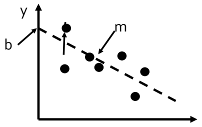
$$\begin{bmatrix} y1 \\ y2 \end{bmatrix} = \underbrace{\begin{bmatrix} 1 & x1 \\ 1 & x2 \end{bmatrix}} * \left.\begin{bmatrix} b \\ m \end{bmatrix}\right\} \text{Two parameters}$$

-One row per subject
-x values are independent variable (age)
-Column of 1’s is the ‘offset’ term (to multiply by *b*)

$$\boxed{\mathbf{Y} = \mathbf{X}*\mathbf{b}} \qquad \mathbf{b} = \begin{bmatrix} b \\ m \end{bmatrix}$$

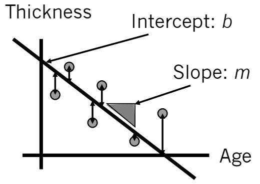
Error

BUT… if we have the same *m* and *b* for all data points, we will have errors:



GOAL: minimize the sum of the square of error terms when estimating our *m* and *b* terms
There are lots of ways to do this! (Beyond the scope of this talk, but FreeSurfer does it for you!)

More than Two Data Points



$$\begin{bmatrix} y1 \\ y2 \\ y3 \\ y4 \end{bmatrix} \boxed{=} \begin{bmatrix} 1 & x1 \\ 1 & x2 \\ 1 & x3 \\ 1 & x4 \end{bmatrix} \boxed{*} \boxed{\begin{bmatrix} b \\ m \end{bmatrix}} \boxed{+} \begin{bmatrix} n1 \\ n2 \\ n3 \\ n4 \end{bmatrix}$$

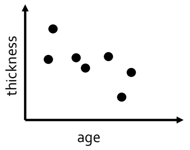
$$\boxed{\mathbf{Y} = \mathbf{X}*\mathbf{b}+\mathbf{n}}$$

y1 = 1**b* + x1**m* + n1
y2 = 1**b* + x2**m* + n2
y3 = 1**b* + x3**m* + n3
y4 = 1**b* + x4**m* + n4

- Model Error
- Noise
- Residuals
- eres.mgh

Forming a Hypothesis

- Now, we can fit our parameters, but we need a hypothesis
- Our example: Is there a significant association between age and thickness?
- **Formal Hypothesis: The slope of age v. thickness (*m*) is significantly different from zero**



Null hypothesis: m = 0

Testing Our Hypothesis

- Once we fit our model for the optimal regression coefficients (m and b), we need to *test them for significance* as well as test the *direction of the effect*
- We do this by forming something called a **contrast matrix** that isolates our parameter of interest
- We can multiply our contrast matrix by our regression coefficient matrix to compute a variable **g,** which tells us the *direction of our effect*
- In this example, since our hypothesis is about the slope *m* we will design our contrast matrix to be **[0 1]**

$$\begin{pmatrix} \text{thickness}_1 \\ \text{thickness}_2 \\ \text{thickness}_3 \\ \text{thickness}_4 \end{pmatrix} = \begin{pmatrix} 1 & \text{age1} \\ 1 & \text{age2} \\ 1 & \text{age3} \\ 1 & \text{age4} \end{pmatrix} * \begin{pmatrix} b \\ m \end{pmatrix} \longrightarrow \quad \mathbf{g = [0\ \ 1]} * \begin{pmatrix} b \\ m \end{pmatrix}$$

If g is negative, then the direction of our effect (slope) is also negative

---

Testing our Hypothesis

- We still need to test for *significance*
- We’ll use our **contrast matrix [0 1]** again here in a *t-test:*

$$t = \frac{\overset{\text{Contrast matrix}}{C} * \overset{\text{Regression coefficients}}{\beta}}{\sqrt{\sigma^2 C * (X^T \underset{\text{Design matrix}}{X})^{-1} C^T}}$$

This t-value corresponds to a **p-value** that depends on your sample size. This **p-value** is between 0 and 1, values closer to 0 indicate a more significant result.

p-values

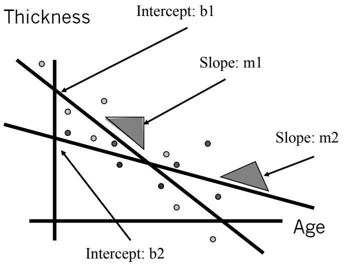
p-value/significance
- value between 0 and 1
- depends on your sample size
- closer to 0 means more significant

FreeSurfer stores p-values as –log10(p):
- $0.1=10^{-1}$→sig=1, $0.01=10^{-2}$→sig=2
- sig.mgh files
- Signed by sign of g
- p-value is for an unsigned test

Putting it all together

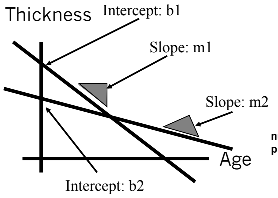
1. We used our empirical data to form a **design matrix: X**
2. We fit **regression coefficients (b and m)** to our x,y data
3. We created a **contrast matrix: C** to test our hypothesis for:
   1. Direction of effect: **g = C*β**
   2. Significance of effect: **t-test**

Two Groups



- Do groups differ in Intercept?
- Do groups differ in Slope?
- Is average slope different from 0?
- …

Two Groups



$$\begin{bmatrix} y11 \\ y12 \\ y21 \\ y22 \end{bmatrix} \boxed{=} \begin{bmatrix} 1 & 0 & x11 & 0 \\ 1 & 0 & x12 & 0 \\ 0 & 1 & 0 & x21 \\ 0 & 1 & 0 & x22 \end{bmatrix} * \begin{bmatrix} b1 \\ b2 \\ m1 \\ m2 \end{bmatrix} + \mathbf{n}$$

number of columns = (number of groups)*(number of parameters)

$$y11 = 1*b1 + 0*b2 + x11*m1 + 0*m2 + n11$$
$$y12 = 1*b1 + 0*b2 + x12*m1 + 0*m2 + n12$$
$$y21 = 0*b1 + 1*b2 + 0*m1 + x21*m2 + n21$$
$$y22 = 0*b1 + 1*b2 + 0*m1 + x22*m2 + n22$$

Two Groups

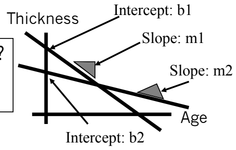
Do groups differ in Intercept?
Does b1=b2?
Does b1-b2 = 0?
C = [+1 -1 0 0], g = **C*****b**

Do groups differ in Slope?
Does m1=m2?
Does m1-m2=0?
C = [0 0 +1 -1], g = **C*****b**

Is average slope different than 0?
Does (m1+m2)/2 = 0?
C = [0 0 0.5 0.5], g = **C*****b**

$$\boxed{\mathbf{Y = X*b+n}}$$

$$\mathbf{b}= \begin{bmatrix} b1 \\ b2 \\ m1 \\ m2 \end{bmatrix}$$



Surface-based Group Analysis in FreeSurfer

- Create your own design and contrast matrices
- Create an FSGD File
  - FreeSurfer creates design matrix
  - You still have to specify contrasts
- QDEC
  - Limited to 2 discrete variables, 2 levels max
  - Limited to 2 continuous variables

Processing Stages

- Specify Subjects and Surface measures
- Assemble Data:
  - Resample into Common Space
  - Smooth
  - Concatenate into one file
- Model and Contrasts (GLM)
- Fit Model (Estimate)
- Correct for multiple comparisons
- Visualize

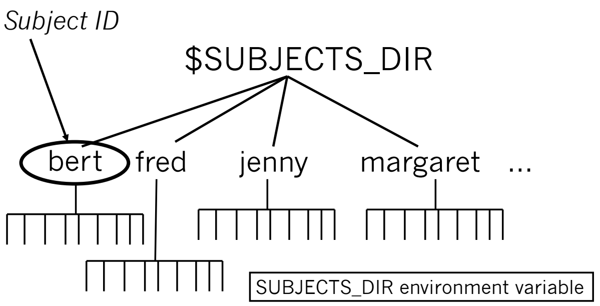
Command-line Processing Stages

- Assemble Data (*mris_preproc*)
  - Resample into Common Space
  - Smooth
  - Concatenate into one file
- Model and Contrasts (GLM) (FSGD)
- Fit Model (Estimate) (*mri_glmfit*)
- Correct for multiple comparisons
- Visualize (freeview/*tksurfer*)

recon-all -qcache

Run <u>after</u> finishing all anatomical analysis, including manual edits.

Specifying Subjects

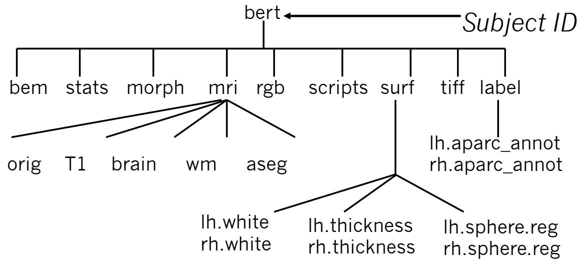

Subject ID

$SUBJECTS_DIR

bert fred jenny margaret …

SUBJECTS_DIR environment variable

FreeSurfer Directory Tree



SUBJECTS_DIR environment variable

Example: Thickness Study

1. $SUBJECTS_DIR/bert/surf/lh.thickness
2. $SUBJECTS_DIR/fred/surf/lh.thickness
3. $SUBJECTS_DIR/jenny/surf/lh.thickness
4. $SUBJECTS_DIR/margaret/surf/lh.thickness
5. …

FreeSurfer Group Descriptor (FSGD) File

- Simple text file
- List of all subjects in the study
- Accompanying demographics
- Automatic design matrix creation
- You must still specify the contrast matrices

Note: *Can* specify design matrix explicitly with --design

FSGD Format

```
GroupDescriptorFile 1
Class Male
Class Female
Variables                    Age   Weight     IQ
Input bert        Male       10    100        1000
Input fred        Male       15    150        1500
Input jenny       Female     20    200        2000
Input margaret    Female     25    250        2500
```

- One Discrete Factor (Gender) with Two Levels (M&F)
- Three Continuous Variables: Age, Weight, IQ

Class = Group

Note: Can *specify* design matrix explicitly with --design

FSGDF → X (Automatic)

Female Group
Male Group
Male Age
Female Age

$$X = \left[\begin{array}{cc|cc|cc|cc} 1 & 0 & 10 & 0 & 100 & 0 & 1000 & 0 \\ 1 & 0 & 15 & 0 & 150 & 0 & 1500 & 0 \\ 0 & 1 & 0 & 20 & 0 & 200 & 0 & 2000 \\ 0 & 1 & 0 & 25 & 0 & 250 & 0 & 2500 \end{array}\right]$$

Age Weight IQ

DODS – Different Offset, Different Slope

Contrasts – You create

Female Group
Male Group
Male Age
Female Age

$$X = \left[\begin{array}{cc|cc|cc|cc} 1 & 0 & 10 & 0 & 100 & 0 & 1000 & 0 \\ 1 & 0 & 15 & 0 & 150 & 0 & 1500 & 0 \\ 0 & 1 & 0 & 20 & 0 & 200 & 0 & 2000 \\ 0 & 1 & 0 & 25 & 0 & 250 & 0 & 2500 \end{array}\right]$$

Age Weight IQ

$$C = [\underbrace{-1\ 1}\ \ 0\ \ 0\ \ 0\ \ 0\ \ 0\ \ 0\,]$$

Tests for the difference in <u>intercept/offset</u> between groups

$$C = [\,0\ 0\ \ \underbrace{-1\ \ 1}\ \ 0\ \ 0\ \ 0\ \ 0\,]$$

Tests for the difference in <u>age slope</u> between groups

Create contrast files with simple text editor

Another FSGD Example

- Two Discrete Factors
  - Gender: Two Levels (M&F)
  - Handedness: Two Levels (L&R)
- One Continuous Variable: Age

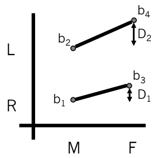
```
GroupDescriptorFile 1
Class MaleRight
Class MaleLeft
Class FemaleRight
Class FemaleLeft
Variables                            Age
Input bert        MaleLeft           10
Input fred        MaleRight          15
Input jenny       FemaleRight        20
Input margaret    FemaleLeft         25
```

Class = Group

Interaction Contrast

- Two Discrete Factors (no continuous, for now)
  - Gender: Two Levels (M&F)
  - Handedness: Two Levels (L&R)
- Four Regressors (Offsets)
  - MR (b_1), ML (b_2), FR (b_3), FL (b_4)

```
GroupDescriptorFile 1
Class MaleRight
Class MaleLeft
Class FemaleRight
Class FemaleLeft
Input bert        MaleLeft
Input fred        MaleRight
Input jenny       FemaleLeft
Input margaret    FemaleRight
```



$$g = D_1 - D_2 \overset{?}{=} 0$$
$$g = (b_3 - b_1) - (b_4 - b_2)$$
$$= -b_1 + b_2 + b_3 - b_4$$
$$C = [-1\ +1\ +1\ -1]$$

Factors, Levels, Groups

Usually each Group/Class:

- Has its own Intercept
- Has its own Slope (for each continuous variable)
- *NRegressors = NClasses * (NVariables+1)* DODS
- *Nregressors = NClasses + Nvariables* DOSS

Why is this important? Because you will need to create contrast matrices, and the contrast matrix must have Nregressor elements.

Factors, Levels, Groups, Classes

Continuous Variables/Factors: Age, IQ, Volume, etc.

Discrete Variables/Factors:
Gender, Handedness, Diagnosis

Levels of Discrete Variables:
- Handedness: *Left and Right*
- Gender: *Male and Female*
- Diagnosis: *Normal, MCI, AD*

Group or Class: Specification of All Discrete Factors
- Left-handed Male MCI
- Right-handed Female Normal

Assemble Data: mris_preproc

mris_preproc --help

```
--fsgd   FSGDFile          : Specify subjects thru FSGD File
--hemi  lh                 : Process left hemisphere
--meas thickness           : subjectid/surf/hemi.thickness
--target fsaverage         : common space is subject fsaverage
--o lh.thickness.mgh       : output "volume-encoded surface file"
```

Lots of other options!

→ Output: lh.thickness.mgh – file with stacked thickness maps for all subjects
→ Input to Smoother or GLM

Surface Smoothing

- mri_surf2surf --help
- Loads stacked lh.thickness.mgh
- 2D surface-based smoothing
- Specify FWHM (eg, fwhm = 10 mm)
- Saves stacked lh.thickness.sm10.mgh
- recon-all –qcache (computes for each subject, run after you are finished editing subject)

---

mri_glmfit

- Reads in FSGD File and constructs **X**
- Reads in your contrasts (**C**1, **C**2, etc.)
- Loads data (lh.thickness.sm10.mgh)
- Fits GLM (ie, computes **b**)
- Computes contrasts (g=**C*****b**)
- t or F ratios, significances
- Significance -log10(p) (.01 → 2, .001 → 3)

---

mri_glmfit

```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

```
mri_glmfit --help
```

---

mri_glmfit

```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

- Input file (output from smoothing).
- Stack of subjects, one frame per subject.

mri_glmfit

```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

- FreeSurfer Group Descriptor File (FSGD)
- Group membership
- Covariates

---

mri_glmfit

```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

- Contrast Matrices
- Simple text/ASCII files
- Test hypotheses
- You must create these by hand!

---

mri_glmfit

```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

- Perform analysis on left hemisphere of fsaverage subject
- Masks by fsaverage cortex.label
- Computes FWHM in 2D

---

mri_glmfit

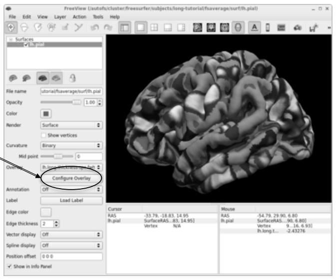
```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

Output directory:

```
lh.gender_age.glmdir/
   beta.mgh – parameter estimates
   rvar.mgh – residual error variance
   etc …
   age/
     sig.mgh – -log10(p), uncorrected
     gamma.mgh, F.mgh
   gender/
     sig.mgh – -log10(p), uncorrected
     gamma.mgh, F.mgh
```

Visualization with freeview

```
freeview –f $FREESURFER_HOME/subjects/fsaverage/surf/
lh.pial:overlay=sig.mgh
```



Use “Configure Overlay” tool to change thresholds for visualization (recall: lower threshold of 1.3 will only display regions where $p<0.05$)

GLM Analysis Using Aseg/Aparc Stats Files

```
mri_glmfit
 --table  aparc_lh_vol_stats.txt
 --fsgd gender_age.txt
 --C age.mtx --C gender.mtx
 --glmdir roi.gender_age.glmdir
```

- Use “--table table.txt” instead of “--y” to specify input
- The rest of the command-line is the same as you would use for a group study (eg, FSGD file and contrasts).
- Output is text file sig.table.dat that lists the significances (-log10(p)) for each ROI and contrast.

Tutorial

Command-line Stream

- Create an FSGD File and contrasts for a thickness study
- Age and Gender
- Run
    - mris_preproc
    - mri_surf2surf
    - mri_glmfit

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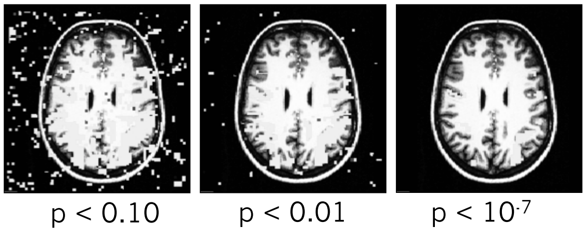
HST Harvard-MIT Health Sciences & Technology

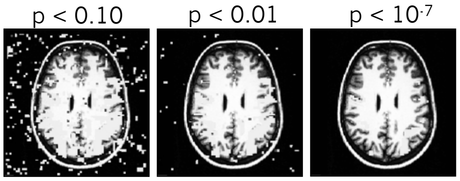
Correction for multiple comparisons in FreeSurfer

Problem of Multiple Comparisons



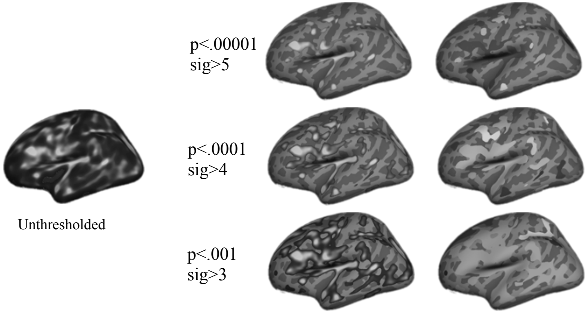
p value is probability that a voxel is falsely activated
- Threshold too liberal: many false positives
- Threshold too restrictive: lose activation (false negatives)

Clusters



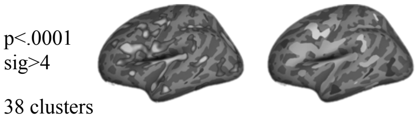
- True signal tends to be clustered
- False Positives tend to be randomly distributed in space
- Cluster – set of spatially contiguous voxels that are above a given threshold.

Cluster-forming Threshold



As threshold lowers, clusters may expand or merge and new clusters can form.
There is no way to say what the threshold is best.

Cluster Table, Uncorrected

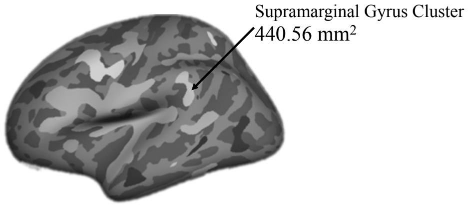


38 clusters

ClusterNo	Area(mm^2)	X	Y	Z	Structure
Cluster 1	3738.82	-11.1	34.5	27.2	superiorfrontal
Cluster 2	5194.19	-32.4	-23.3	15.7	insula
Cluster 3	1271.30	-25.9	-75.0	19.0	superiorparietal
Cluster 4	775.38	-44.4	-9.7	51.3	precentral
Cluster 5	440.56	-33.0	-36.8	37.5	supramarginal
…					

How likely is it to get a cluster of a certain size under the null hypothesis?

Clusterwise Correction

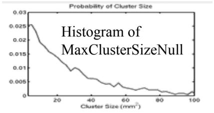


How likely is it to get a cluster 440.56mm^2 or bigger by chance?
How likely is it to get a cluster of a certain size under the null hypothesis?

Cluster-based Correction for Multiple Comparisons

1. Simulate data under Null Hypothesis:
   - Synthesize Gaussian noise and then smooth (Monte Carlo)
   - Permute rows of design matrix (Permutation, orthog.)
2. Analyze, threshold, cluster, get MaxClusterSizeNull
3. Repeat 10,000 times – gives a list of 10000 MaxClusterSizeNulls under the null
4. Analyze real data, get ClusterSize (eg, 440.56 mm2)
5. Count number of times MaxClusterSizeNull > ClusterSize

P(cluster) = #(MaxClusterSizeNull > ClusterSize) /10000

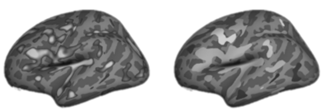


Histogram of MaxClusterSizeNull

mri_glmfit-sim

Cluster Table, Corrected

p<.0001
sig>4

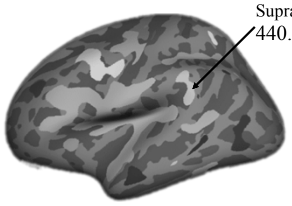


22 clusters out of 38 have cluster p-value < .05

ClusterNo	Area(mm^2)	X	Y	Z	Structure	Cluster P
Cluster 1	3738.82	-11.1	34.5	27.2	superiorfrontal	.0001
Cluster 2	5194.19	-32.4	-23.3	15.7	insula	.0003
Cluster 3	1271.30	-25.9	-75.0	19.0	superiorparietal	.0050
Cluster 4	775.38	-44.4	-9.7	51.3	precentral	.0100
Cluster 5	440.56	-33.0	-36.8	37.5	supramarginal	.0400
…						

Note the difference between the Cluster Forming Threshold (p<.0001) and the Clusterwise p-value (.05).

Clusterwise Correction



Supramarginal Gyrus Cluster
440.56 mm^2

Probability of getting a cluster 440.56mm^2 or bigger by chance is p=.04
This is the clusterwise p-value.

Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir lh.gender_age.glmdir
  --cache 2 pos
  --2spaces
  --cwpvalthresh .05
```

Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir lh.gender_age.glmdir
  --cache 2 pos
  --2spaces
  --cwpvalthresh .05
```

<u>Original mri_glmfit command:</u>

```
mri_glmfit
  --y lh.thickness.sm10.mgh
  --fsgd gender_age.txt
  --C age.mtx –C gender.mtx
  --surf  fsaverage lh
  --cortex
  --glmdir lh.gender_age.glmdir
```

```
lh.gender_age.glmdir/
   beta.mgh – parameter estimates
   rvar.mgh – residual error variance
   age/
     sig.mgh – -log10(p), uncorrected
     gamma.mgh, F.mgh
   gender/
     sig.mgh – -log10(p), uncorrected
     gamma.mgh, F.mgh
```

Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir lh.gender_age.glmdir
  --cache 2 pos
 --2spaces
 --cwpvalthresh . 05
```

- Use pre-computed simulation results
- positive contrast
- voxelwise threshold thres = 2 (p<.01)
- Can do another simulation or permutation
- Not related to recon-all -qcache

Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir lh.gender_age.glmdir
  --cache 2 pos
  --cwpvalthresh .05
  --2spaces
```

Cluster-wise threshold p<.05
cw = cluster-wise
pval = p value
thresh = threshold

Surface-based Correction for Multiple Comparisons

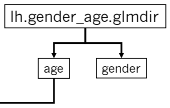
- 2D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir lh.gender_age.glmdir
  --cache 2 pos
  --cwpvalthresh .05
  --2spaces
```

Doing analysis with left hemi but right hemi will be done separately. Need to correct for full search space.

Correction for Multiple Comparisons Output

```
mri_glmfit-sim
  --glmdir lh.gender_age.glmdir
  --cache 2 pos
  --cwpvalthresh .05
  --2spaces
```



sig.mgh – pre-existing uncorrected p-values
cache.th20.pos.sig.cluster.mgh – map of significance of clusters
cache.th20.pos.sig.ocn.annot – annotation of significant clusters
cache.th20.pos.sig.cluster.summary – text file of cluster table (clusters, sizes, MNI305 XYZ, and their significances)

- Only shows clusters p<.05, change –cwpvalthesh to a larger value to get more (ie, less sig) clusters

Corrected Outputs

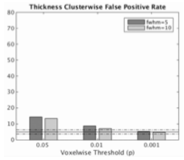
cache.th20.pos.sig.ocn.annot – annotation of significant clusters

cache.th20.pos.sig.cluster.summary -- text file of cluster table

```
ClusterNo  Area(mm2)  X      Y      Z     Structure         Cluster P
Cluster 1   3738.82  -11.1  34.5  27.2  superiorfrontal   .0001
Cluster 2   5194.19  -32.4 -23.3  15.7  insula            .0003
Cluster 3   1271.30  -25.9 -75.0  19.0  superiorparietal  .0050
Cluster 4    775.38  -44.4  -9.7  51.3  precentral        .0100
Cluster 5    440.56  -33.0 -36.8  37.5  supramarginal     .0400
…
```

Eklund, et al, 2016 PNAS

- High false positive rates using resting state fMRI analyzed as task data
- Caused by non-Gaussian smoothness
- Applies to parametric (random field theory) and Monte Carlo simulations
- Effect present in thickness analysis, but not as bad



Eklund fMRI results were in the range of 10-60% false positive rate.

Cluster Failure: Why fMRI inferences for spatial extent have inflated false-positive rates. Eklund, Nichols, Knutsson, 2016. PNAS

Permutation

mri_glmfit-sim –perm <nsim> <vthresh> <sign>

- If there is no effect of group, then group membership can be randomly changed.
  - Repeat this many times to get NULL distribution
- Makes no assumptions about smoothness or Gaussianity of the data.
- Requires designs without nuisance vars (age)

Example command:

```
mri_glmfit-sim –perm 10000 2 pos
```

Output files are the same (prepended with “perm.”)

False Discover Correction Possible

- False Discovery Rate (FDR)
  - Built into tksurfer & QDEC
    (Genovese, et al, NI 2002)
- mri_fdr --help

Tutorial

1. Command-line Stream
   - Create an FSGD File for a thickness study
   - Age and Gender
   - Run
     - mris_preproc
     - mri_surf2surf
     - mri_glmfit
     - mri_glmfit-sim
     - tksurfer
2. QDEC – same data set

QDEC – An Interactive Statistical Engine GUI

Query – Select subjects based on Match Criteria
Design – Specify discrete and continuous factors
Estimate – Fit Model
Contrast – Automatically Generate Contrast Matrices

Interactive – Makes easy things easy (that used to be hard)

...a work in progress
- No Query yet
- Two Discrete Factors (Two Levels)
- Two Continuous Factors
- Surface only

-qcache

For QDEC to work interactively, you need to run:

recon-all -s <sid> -qcache

(or as additional flag in your regular processing)

This will map and smooth **thickness** maps to **fsaverage**,
use *–target <id>* to specify your own target
and *–measure <surfmeas>* to specify curv, area, sulc etc.

QDEC – Spreadsheet

qdec.table.dat – spreadsheet with subject information – can be huge!

fsid	gender	age	diagnosis	Left-Cerebral-White-Matter-Vol
011121_vc8048	Female	70	Demented	202291
021121_62313-2	Female	71	Demented	210188
010607_vc7017	Female	73	Nondemented	170653
021121_vc10557	Male	75	Demented	142029
020718_62545	Male	76	Demented	186087
020322_vc8817	Male	77	Nondemented	149810

gender.levels

Female
Male

diagnosis.levels

Demented
Nondemented

Discrete Factors need a factorname.level file

QDEC GUI

Design Name: Untitled

Discrete (choose up to two):
gender

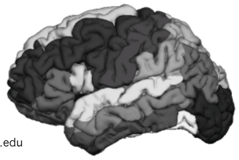
Continuous (choose up to two):
age
Left-Hippocampus
Right-Hippocampus

Measure: thickness
Hemisphere: lh
Smoothing (FWHM): 10

- Load QDEC Table File
  - List of Subjects
  - List of Factors (Discrete and Cont)
- Choose Factors
- Choose Input (cached):
  - Hemisphere
  - Measure (eg, thickness)
  - Smoothing Level
- “Analyze”
  - Builds Design Matrix
  - Builds Contrast Matrices
  - Constructs Human-Readable Questions
  - Analyzes
  - Displays Results

- freesurfer.net

Longitudinal FreeSurfer



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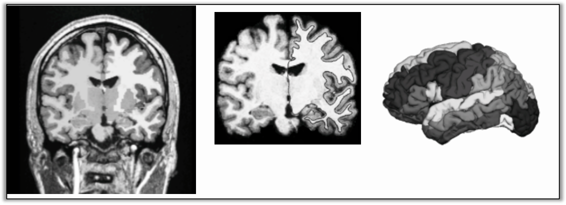
http://reuter.mit.edu

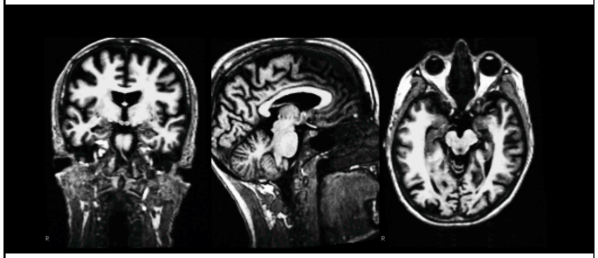
MGH/HST Athinoula A. Martinos
Center for Biomedical Imaging

What can we do with FreeSurfer?

- measure volume of cortical or subcortical structures
- compute thickness (locally) of the cortical sheet
- study differences of populations (diseased, control)



Neurodegenerative disease:



14 time points, 6 years, Huntington's Disease

We'd like to:

- exploit longitudinal information
  (same subject, different time points)

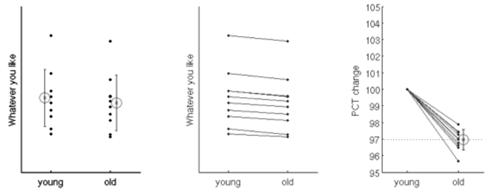
Why longitudinal?

- to reduce variability on intra-individual morph estimates
- to detect small changes, or use less subjects (power)
- for marker of disease progression (atrophy)
- to better estimate time to onset of symptoms
- to study effects of drug treatment

…

Example 1

Example 2



Challenges in Longitudinal Designs

1. **Over-Regularization:**
   - Temporal smoothing
   - Non-linear warps
   - ❖ Potentially underestimating change
2. **Bias**
   - Interpolation Asymmetries [Yushkevich et al. 2010]
   - Asymmetric Information Transfer
   - ❖ Often overestimating change
3. **Limited designs:**
   - Only 2 time points
   - Special purposes (e.g. only surfaces, WM/GM)

How can it be done?

- Stay *unbiased* with respect to any specific time point by treating all the same
- Create a within subject *template* (base) as an initial guess for segmentation and reconstruction
- *Initialize* each time point with the template to reduce variability in the optimization process
- For this we need a **robust registration** (rigid) and **template estimation**

Reuter et al. NeuroImage 2011 & 2012

Robust Registration

Goal: Highly accurate inverse consistent registrations

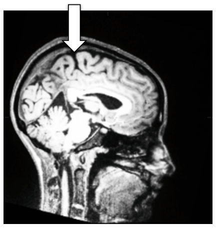
- In the **presence** of:
  - Noise
  - Gradient non-linearities
  - Movement: jaw, tongue, neck, eye, scalp ...
  - Cropping
  - Atrophy (or other longitudinal change)

We need:

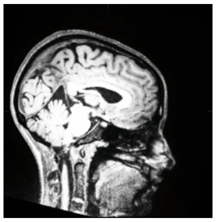
- **Inverse consistency** keep registration **unbiased**
- **Robust statistics** to **reduce** influence of outliers

Reuter, Rosas, Fischl. NeuroImage 2010

Robust Registration

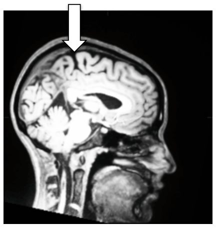


Target

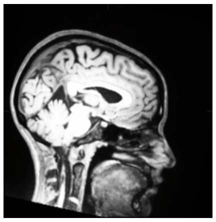


Target

Robust Registration



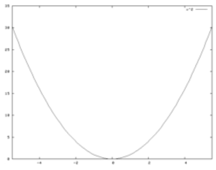
Registered Src FSL FLIRT



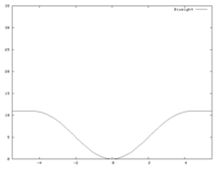
Registered Src Robust

Robust Registration

Limited contribution of outliers *[Nestares&Heeger 2000]*

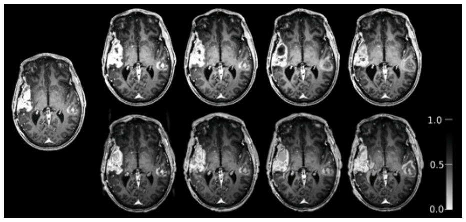


Square



Tukey's Biweight

Robust Registration



Tumor data with significant intensity differences in the brain, registered to first time point (left).

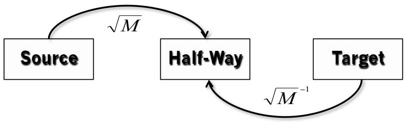
Robust Registration

Inverse consistency:

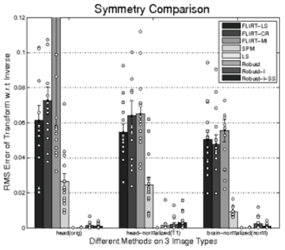
- a **symmetric displacement** model:

$$r(p) = I^T\left(\bar{x} - \frac{1}{2}\bar{d}(\bar{p})\right) - I^S\left(\bar{x} + \frac{1}{2}\bar{d}(\bar{p})\right)$$

- resample both source and target to an **unbiased half-way space** in intermediate steps (matrix square root)



Robust Registration



Inverse consistency of different methods on original (orig), intensity normalized (T1) and skull stripped (norm) images.

LS and Robust:

- nearly perfect symmetry (worst case RMS < 0.02)

Other methods:

- several alignments with RMS errors > 0.1

Robust Registration

- *mri_robust_register* is part of FreeSurfer
- can be used for pair-wise registration (optimally within subject, within modality)
- can output results in half-way space
- can output 'outlier-weights'
- see also *Reuter et al., NeuroImage 2010* for comparison with FLIRT (FSL) and SPM coreg
- for more than 2 images use**:** *mri_robust_template*

Robust Template Estimation

- Minimization problem for N images:

$$\{\hat{I}, \hat{\varphi}_i\} := \operatorname*{argmin}_{I, \varphi_i} \sum_{i=1}^{N} E(I_i \circ \varphi_i, I) + D(\varphi_i)^2$$

- Image Dissimilarity:

$$E(I_1, I_2) = \int_\Omega |I_1(x) - I_2(x)|\, dx$$

- Metric of Transformations:

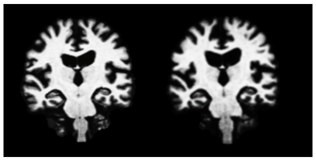
$$D(\vec{t}, r)^2 = \| \vec{t} \|^2 + \| R - \mathbf{1} \|_F^2$$

Reuter, Rosas, Fischl. NeuroImage 2012

Challenges

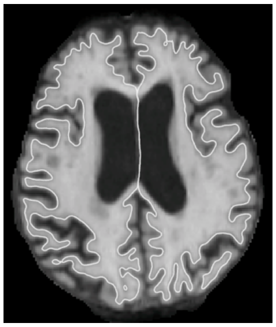
1. **Over-Regularization (limited flexibility):**
   - ➢ Will avoid by only initializing processing
2. **Bias** [Reuter and Fischl 2011] , [Reuter et al. 2012]
   - ➢ Will avoid by treating time points the same
3. **Limited designs:**
   - ➢ Allow n time points
   - ➢ Reliably estimate all of FS measurements

(i) Interpolation Asymmetries (Bias)

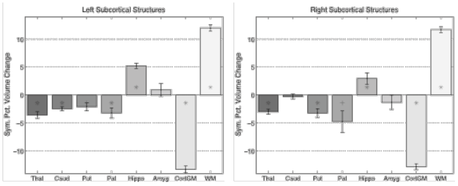


Mapping follow-up to baseline:

- Keeps baseline image fixed (crisp)
- Causes interpolation artefacts in follow-up (smoothing)
- Often leads to overestimating change



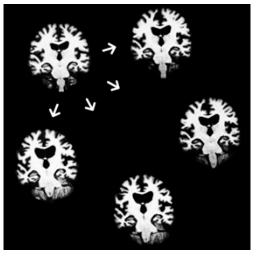
(i) Interpolation Asymmetries (Bias)



MIRIAD dataset: 65 subjects
First session first scan compared to twice interpolated image.
Regional: not finding it does not mean it is not there.

http://miriad.drc.ion.ucl.ac.uk

(ii) Asymmetric Information Transfer



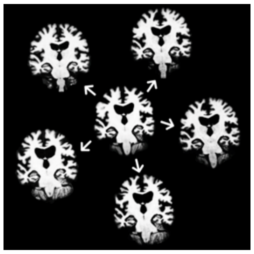
Example:

1. Process baseline
2. Transfer results from baseline to follow-up
3. Let procedures evolve in follow-up

(or construct skullstrip in baseline, or Talairach transform …)

<u>Can introduce bias!</u>

Robust Unbiased Subject Template



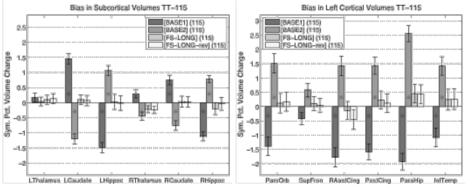
1. Create subject template (iterative registration to median)
2. Process template
3. Transfer to time points
4. Let it evolve there

- All time points are treated the same
- Minimize over-regularization by letting tps evolve freely

Reuter et al. OHBM 2010, NeuroImage 2011 & 2012

(ii) Asymmetric Information Transfer

<u>Test-Retest (115 subjects, 2 scans, same session)</u>



Subcortical Cortical

Biased information transfer: [BASE1] and [BASE2].
Our method [FS-LONG] [FS-LONG-rev] shows no bias.

Review the central ideas

Idea: *Would like to include some information that much of the anatomy is the same over time, but don't want to lose sensitivity to disease effects.*

How to minimize over regularization:

- ✓ Only initialize processing, evolve freely

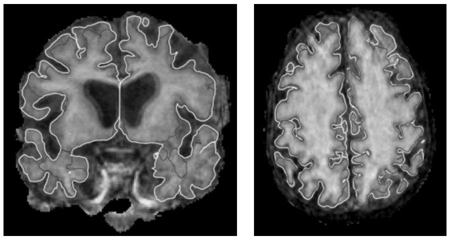
How to avoid processing bias:

- ✓ Treat all time points the same

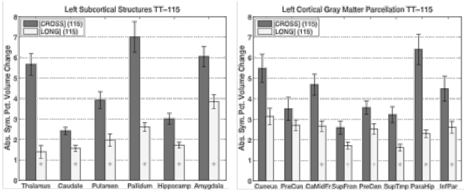
Why not simply do independent processing then?

- ➢ Sharing information across time points increases reliability, statistical power!

Improved Surface Placement



Test-Retest Reliability



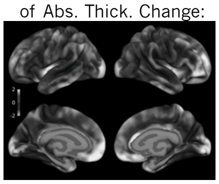
Subcortical Cortical

[LONG] significantly improves reliability
115 subjects, MEMPRAGE, 2 scans, same session

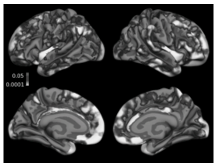
Reuter et al. NeuroImage 2012

Test-Retest Reliability

Diff. ([CROSS]-[LONG])
of Abs. Thick. Change:

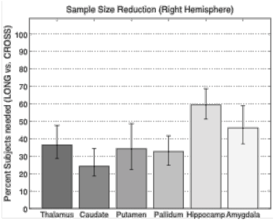


Significance Map



[LONG] significantly improves reliability
115 subjects, ME MPRAGE, 2 scans, same session

Increased Power

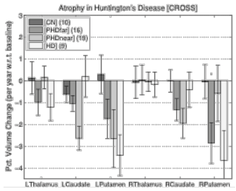


Sample Size Reduction when using [LONG]
(based on test-retest 14 subjects, 2 weeks)

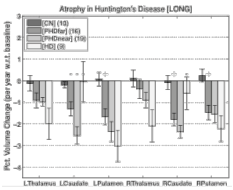
Huntington's Disease (3 visits)

(with D. Rosas)

Independent Processing



Longitudinal Processing

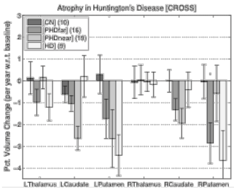


[LONG] shows higher precision and better discrimination power between groups (specificity and sensitivity).

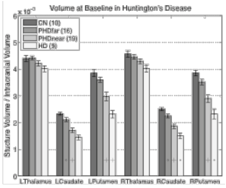
Huntington's Disease (3 visits)

(with D. Rosas)

Rate of Atrophy

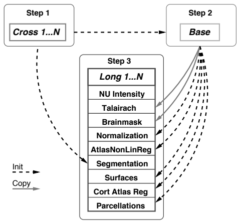


Baseline Vol. (normalized)



Putamen Atrophy Rate can is significantly different between CN and PHD far, but baseline volume is not.

Robust Template for Initialization



- Unbiased
- Reduces Variability
- Common space for:
  - TIV estimation
  - Skullstrip
  - Affine Talairach Registration
- Basis for:
  - Intensity Normalization
  - Non-linear Registration
  - Surfaces / Parcellation

FreeSurfer Commands (recon-all)

1. CROSS (independently for each time point tpNid):

```
recon-all -subjid tpNid -all
```

2. BASE (creates template, one for each subject):

```
recon-all -base baseid -tp tp1id \
      -tp tp2id ... -all
```

3. LONG (for each time point tpNid, passing baseid):

```
recon-all -long tpNid baseid -all
```

This creates the final directories **tpNid.long.baseid**

Directory Structure

Contains all CROSS, BASE and LONG data:

- me1
- me2
- me3
- me_base
- me1.long.me_base
- me2.long.me_base
- me3.long.me_base
- you1
- …

Single time point

Since FS5.2 you can run subjects with a single time point through the longitudinal stream!

- Mixed effects models can use single time point subjects to estimate variance (increased power)
- This assures identical processing steps as in a subject with several time points
- Commands same as above:

```
recon-all -subjid tp1id -all
recon-all -base baseid -tp tp1id -all
recon-all -long tp1id baseid -all
```

Final Remarks …

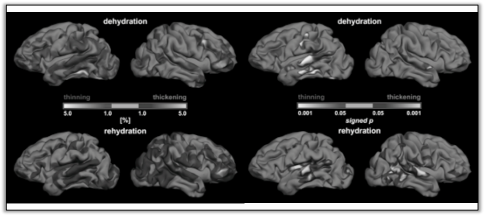
Sources of Bias during Acquisition

BAD: influence images directly and cannot be easily removed!

- **Different Scanner Hardware** (Headcoil, Pillow?)
- **Different Scanner Software** (Shimming Algorithm)
- **Scanner Drift and Calibration**
- **Different Motion Levels Across Groups**
- **Different Hydration Levels** (season, time of day)

Hydration Levels

14 subjects, 12h dehydration (over night)



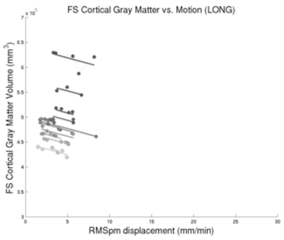
rehydration 1L/h

Biller et al. American Journal of Neuroradiology 2015

Motion Biases GM Estimates

- 12 volunteers
- 5 motion types:
  - 2 Still
  - Nod
  - Shake
  - Free
- Duration:
  - 5-15 s/min

Effect:
roughly 0.7-1% volume loss per 1mm/min increase in motion



Reuter, et al., NeuroImage 2014

Still to come …

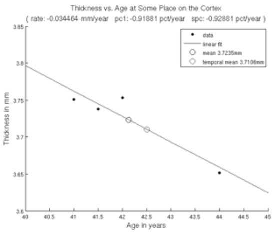
- Common warps (non-linear)
- Optimized intracranial volume estimation
- Joint intensity normalization
- New thickness computation
- Joint spherical registration

http://freesurfer.net/fswiki/**LongitudinalProcessing**

Longitudinal Tutorial

1. How to process longitudinal data
   - Three stages: CROSS, BASE, LONG
2. Post-processing (statistical analysis):
   - (i) compute atrophy rate within each subject
   - (ii) group analysis (average rates, compare)
   - here: two time points, rate or percent change
3. Manual Edits
   - Start in CROSS, do BASE, then LONGs should be fixed automatically
   - Often it is enough to just edit the BASE
   - See http://freesurfer.net/fswiki/LongitudinalEdits

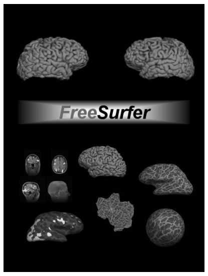
Longitudinal Tutorial



- Temporal Average
- Rate of Change
- Percent Change (w.r.t. time 1)
- Symmetrized Percent Change (w.r.t. temp. avg.)

FreeSurfer: Troubleshooting

surfer.nmr.mgh.harvard.edu



MASSACHUSETTS
GENERAL HOSPITAL

Hard and Soft Failures

Categories of errors: Hard & Soft Failures

•Hard = recon-all quits before it finishes

•Soft = recon-all finishes but results need modification
(i.e. surface or segmentation inaccuracy)

-recon-all takes a long time (3-20 hours) to run & some part of the process may need modification
(e.g. cerebellum removed in skull stripping)

Troubleshooting: Soft Failures

- Some Examples of soft failures:
  - Skull Strip Errors
  - WM/ASEG Segmentation Errors
  - Intensity Normalization Errors
  - Pial Surface misplacement
  - Topological Defect incorrectly fixed

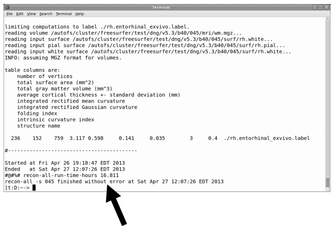
Upon Completion of recon-all…

bert

scripts mri surf label stats

recon-all.log

<u>recon-all.done</u>



```
limiting computations to label ./rh.entorhinal_exvivo.label.
reading volume /autofs/cluster/freesurfer/test/dng/v5.3/b40/045/mri/wm.mgz...
reading input surface /autofs/cluster/freesurfer/test/dng/v5.3/b40/045/surf/rh.white...
reading input pial surface /autofs/cluster/freesurfer/test/dng/v5.3/b40/045/surf/rh.pial...
reading input white surface /autofs/cluster/freesurfer/test/dng/v5.3/b40/045/surf/rh.white...
INFO: assuming MGZ format for volumes.

table columns are:
    number of vertices
    total surface area (mm^2)
    total gray matter volume (mm^3)
    average cortical thickness +- standard deviation (mm)
    integrated rectified mean curvature
    integrated rectified Gaussian curvature
    folding index
    intrinsic curvature index
    structure name

  236    152    759  3.117 0.598     0.141     0.035        3     0.4  ./rh.entorhinal_exvivo.label

#-----------------------------------------

Started at Fri Apr 26 19:18:47 EDT 2013
Ended   at Sat Apr 27 12:07:26 EDT 2013
#@#%# recon-all-run-time-hours 16.811
recon-all -s 045 finished without error at Sat Apr 27 12:07:26 EDT 2013
[t:D:~-> 
```

Just because it finishes "without error" does not mean that everything is ok!

Could be a "soft" failure.

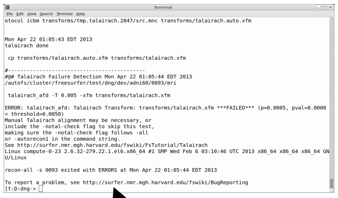
Troubleshooting: Hard Failures

bert

scripts mri surf label stats

recon-all.log

<u>recon-all.error</u>



```
otocol icbm transforms/tmp.talairach.2847/src.mnc transforms/talairach.auto.xfm


Mon Apr 22 01:05:43 EDT 2013
talairach done

 cp transforms/talairach.auto.xfm transforms/talairach.xfm

#---------------------------------------------
#@# Talairach Failure Detection Mon Apr 22 01:05:44 EDT 2013
/autofs/cluster/freesurfer/test/dng/dev/adni60/0093/mri

 talairach_afd -T 0.005 -xfm transforms/talairach.xfm

ERROR: talairach_afd: Talairach Transform: transforms/talairach.xfm ***FAILED*** (p=0.0005, pval=0.0000
< threshold=0.0050)
Manual Talairach alignment may be necessary, or
include the -notal-check flag to skip this test,
making sure the -notal-check flag follows -all
or -autorecon1 in the command string.
See http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/Talairach
Linux compute-0-23 2.6.32-279.22.1.el6.x86_64 #1 SMP Wed Feb 6 03:10:46 UTC 2013 x86_64 x86_64 x86_64 GN
U/Linux

recon-all -s 0093 exited with ERRORS at Mon Apr 22 01:05:44 EDT 2013

To report a problem, see http://surfer.nmr.mgh.harvard.edu/fswiki/BugReporting
[t:D:dng-> 
```

- Ran out of disk space?
- Ran out of RAM?
- Unix file permissions?
- Pathological conditions (brain, artifact)
- Sunspots??????

Send us recon-all.log
freesurfer@nmr.mgh.harvard.edu

Hard Failure: What to do

- Check recon-all.log for error message
- Examine data quality
- Rerun step that failed
- Verify output from last successful step
- Search FreeSurfer mailing list for this problem
- Run modified version of command if needed
- Email the mailing list

Hard Failure: Help Us Help You!

- Report version currently using
  - see top of recon-all.log
  - cat $FREESURFER_HOME/build-stamp.txt
- Operating System/hardware
- Exact command-line tried to run
- Send recon-all.log
- Output from terminal window if appropriate

(Nick even has a command to help – bugr)

Soft Failures

- recon-all finishes but surfaces or aseg not accurate
- It is not possible to directly edit the location of a surface.
- When the surfaces are inaccurate, you have to (manually) change the information in a volume and regenerate the surface.

Check Your Recon for Accuracy

- Do your surfaces follow gm/wm borders?
- Does the subcortical segmentation follow intensity boundaries?

Unfortunately we almost never have access to ground truth in imaging.

(editorial note: ALL morphometry packages make errors. FS allows you to correct these errors. This feature is not available in other packages.)

Manual Interventions

1. Erase voxels
2. Fill voxels
3. Clone voxels (ie, copy from one volume to another)
4. Add "Control Points"

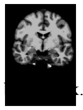
Manual interventions should take less than 30min
After manual intervention, re-run parts of recon-all

It is also possible to re-run recon-all with different parameters which is good for systematic or large errors

Manual Edits Applied to Volumes not Surfaces

bert

- scripts
- mri
- surf
- label
- stats



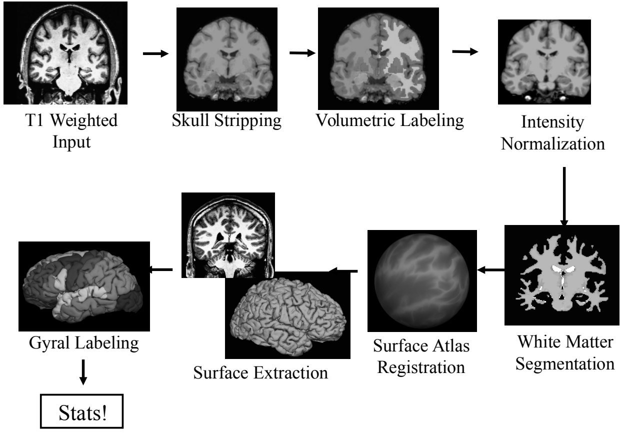
.mgz

wm.mgz

	Erase	Fill	Clone to	Control Points
brainmask	X		X	X
wm	X	X		

*Other volumes involved in QA: brain.finalsurfs, norm.mgz, T1.mgz

Processing Stream Overview



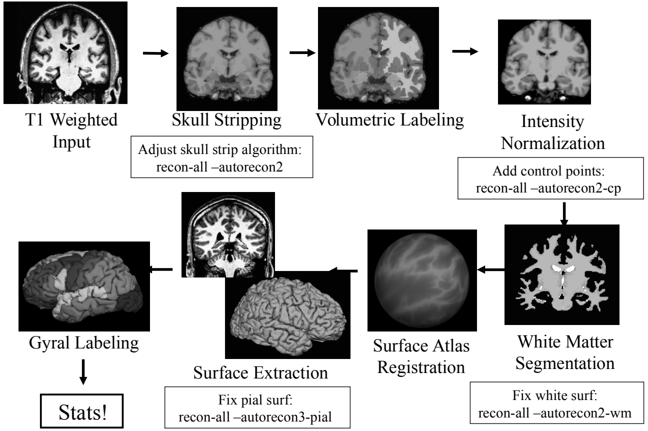
Reconstruction Stages

recon-all is broken into three stages

- autorecon1
- autorecon2
- autorecon3

these 3 stages are equivalent to -all

Processing Stream Overview



T1 Weighted Input

Skull Stripping

Adjust skull strip algorithm:
recon-all –autorecon2

Volumetric Labeling

Intensity Normalization

Add control points:
recon-all –autorecon2-cp

White Matter Segmentation

Fix white surf:
recon-all –autorecon2-wm

Surface Atlas Registration

Surface Extraction

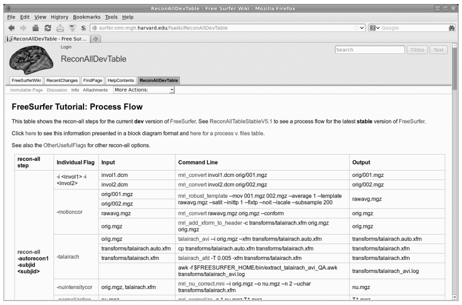
Fix pial surf:
recon-all –autorecon3-pial

Gyral Labeling

Stats!

Processing Stream Order

http://surfer.nmr.mgh.harvard.edu/fswiki/ReconAllDevTable



FreeSurfer Tutorial: Process Flow

This table shows the recon-all steps for the current **dev** version of FreeSurfer. See ReconAllTableStableV5.1 to see a process flow for the latest **stable** version of FreeSurfer.

Click here to see this information presented in a block diagram format and here for a process v. files table.

See also the OtherUsefulFlags for other recon-all options.

recon-all step	Individual Flag	Input	Command Line	Output
recon-all **-autorecon1 -subjid <subjid>**	-i <invol1> -i <invol2>	invol1.dcm	mri_convert invol1.dcm orig/001.mgz	orig/001.mgz
		invol2.dcm	mri_convert invol2.dcm orig/002.mgz	orig/002.mgz
	-motioncor	orig/001.mgz orig/002.mgz	mri_robust_template --mov 001.mgz 002.mgz --average 1 --template rawavg.mgz --satit --inittp 1 --fixtp --noit --iscale --subsample 200	rawavg.mgz
		rawavg.mgz	mri_convert rawavg.mgz orig.mgz --conform	orig.mgz
		orig.mgz	mri_add_xform_to_header -c transforms/talairach.xfm orig.mgz orig.mgz	orig.mgz
	-talairach	orig.mgz	talairach_avi --i orig.mgz --xfm transforms/talairach.auto.xfm	transforms/talairach.auto.xfm
		transforms/talairach.auto.xfm	cp transforms/talairach.auto.xfm transforms/talairach.xfm	transforms/talairach.xfm
		transforms/talairach.xfm	talairach_afd -T 0.005 -xfm transforms/talairach.xfm	transforms/talairach.xfm
			awk -f $FREESURFER_HOME/bin/extract_talairach_avi_QA.awk transforms/talairach_avi.log	transforms/talairach_avi.log
	-nuintensitycor	orig.mgz, talairach.xfm	mri_nu_correct.mni --i orig.mgz --o nu.mgz --n 2 --uchar transforms/talairach.xfm	nu.mgz

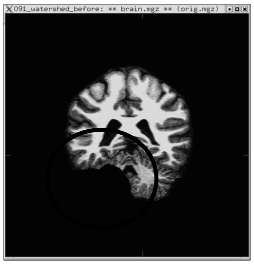
---

Or Make Life Easier

recon-all -make all -s subjid

Skull Strip Failure: Too Much Removed

T1.mgz



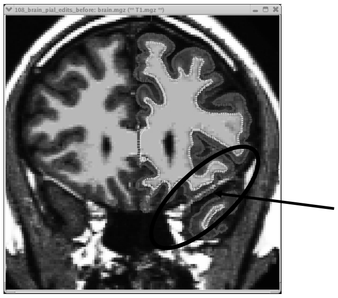
brainmask.mgz

Use "clone" tool to manually correct, or adjust watershed parameters and run (default wsthresh is 25, higher means strip less):

recon-all -skullstrip -wsthresh 35 -clean-bm -no-wsgcaatlas -s <subj>

recon-all -s <subject> -autorecon2 -autorecon3

Skull Strip Failure: Not enough Removed



Dura or blood vessel.
the white surface is OK, but
the pial surface is inaccurate

Dura and GM have extremely similar intensity characteristics on most T1-weighted sequences (but different T2*!). Typical fix: edit the brainmask.mgz to erase dura/blood vessels, and run:

recon-all -s <subject> -autorecon-pial

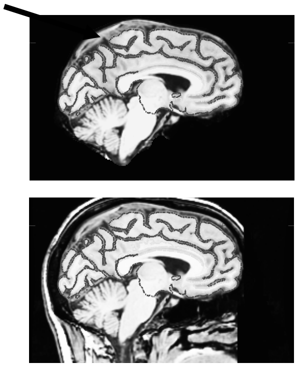
Skull Strip Failure: Not Enough Removed

Eye Socket classified as WM due to Skull Strip Failure.
Erase in wm.mgz then run:

```
recon-all   -s <subject>  -autorecon2-wm   -autorecon3
```

This is NOT a Skull Strip Error

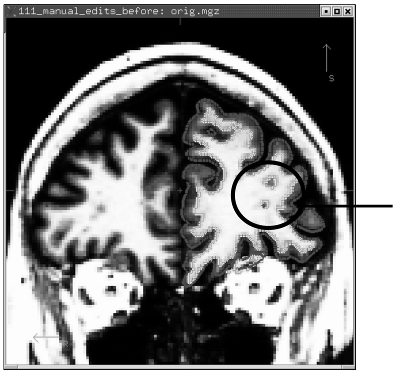
It appears that the skull strip left a lot of dura. It did, but it does not affect the surface, so leave it!



Segmentation Errors

- White Matter classified as non-White Matter
- Gray Matter classified as White Matter
- Causes:
  - Intensity Normalization Failures
  - Partial voluming

Segmentation Error



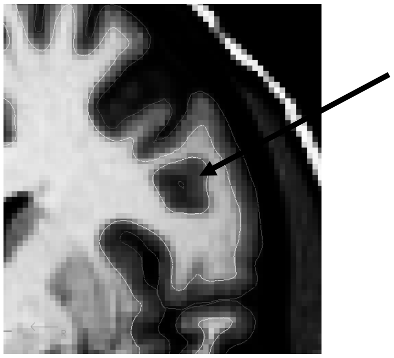
“Hypo-Intensities” White Matter Lesions Misclassified as gray matter

wm.mgz

Fill in wm.mgz then run:

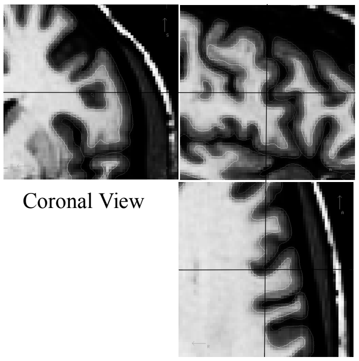
```
recon-all   -s <subject>  -autorecon2-wm   -autorecon3
```

Is this a segmentation error?



Coronal View

This is NOT an an error.



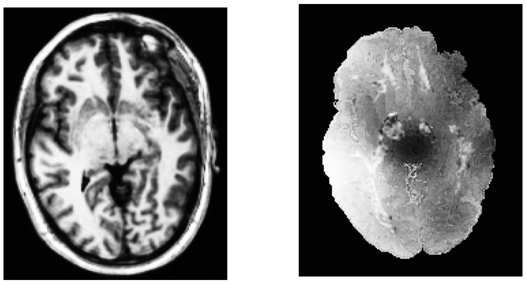
Sagittal View

Coronal View

Axial View

Make sure to look at all 3 views before deciding!

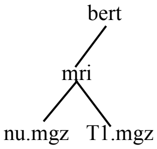
Intensity Bias

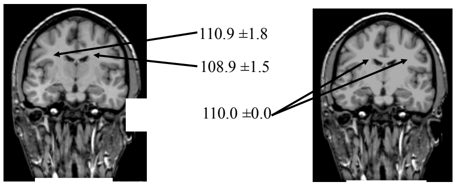


- One side of the image much brighter than the other side
- Worse with many coils
- Makes gray/white segmentation difficult

Intensity Normalization

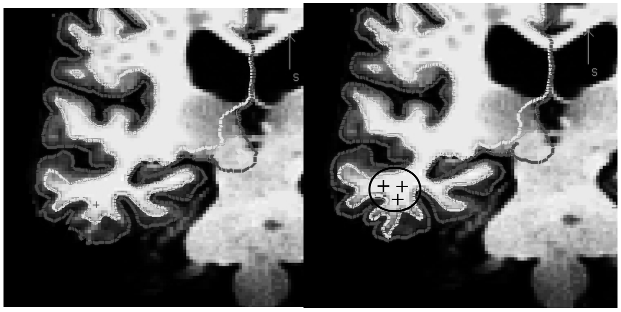
- Removes B1 bias field
- NU (MNI) nu.mgz
- Presegmentation (T1.mgz)
  - Most WM = 110 intensity
  - Pre- and Post-Skull Strip





nu.mgz T1.mgz

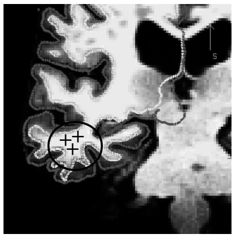
Troubleshooting: Intensity Normalization



Intensity Normalization Failure. Most WM in T1 volume (T1.mgz) should be close to 110. Can fix by editing wm.mgz or adding **“Control Points” (+)**. Beware partial voluming!

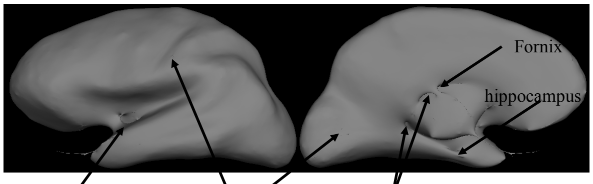
```
recon-all   -s <subject>   -autorecon2-cp   -autorecon3
```

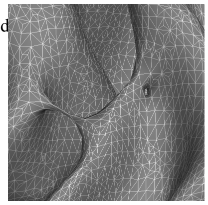
Control Points: Summary



- Used to rescale intensity near the control point
- Must go in voxels that are fully WM but not 110 !!!
- Use sparingly
- Can be created viewing any volume
- Saved in a separate text file (e.g., bert/tmp/control.dat)

Segmentation Errors: Topological Defects



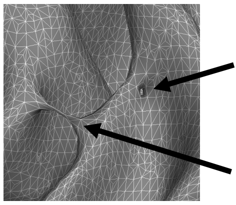


- Holes, Handles
- Automatically Fixed
- Not always fixed correctly
- Edit wm.mgz

Topology Correction

BEFORE AFTER

Segmentation Errors: Topological Defects



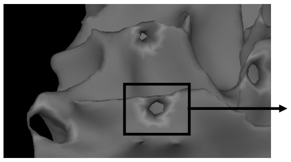
Hole: Partial Voluming: WM + GM looks like non-WM, it is segmented as non-WM and creates a hole

Handle: Something bright in a sulcus that gets classified as WM.

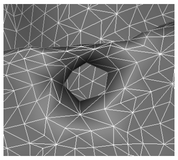
Holes: fill voxels in the wm.mgz
Handles: erase voxels in the wm.mgz

wm.mgz

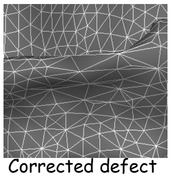
Automatic Defect Correction



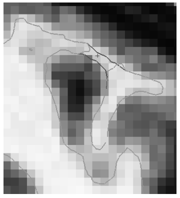
Initial cortical surface



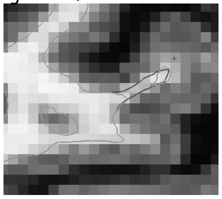
Topological defect



Corrected defect

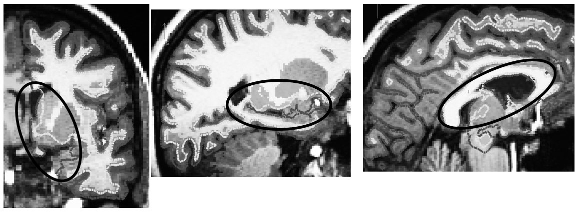


Sagittal view

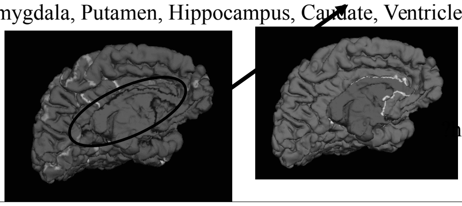


Coronal view

Noncortical Regions: These are not errors

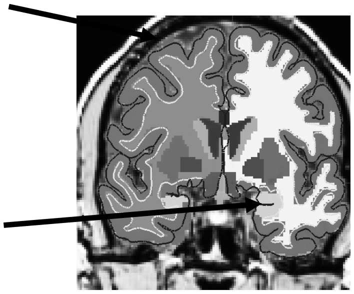


Amygdala, Putamen, Hippocampus, Caudate, Ventricles, CC



.cortex.label

These are NOT errors



It appears that the aseg cortical ribbon is inaccurate. It is, but the aseg cortical ribbon is not used for anything!

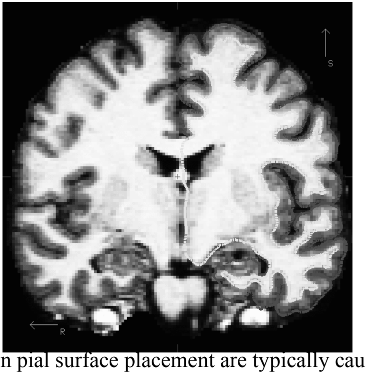
Surfaces are not valid in subcortical regions along the medial wall.

It is possible to edit the segmentation.

How Do You Know What to Edit?

- If pial surface includes too much:
  - edit brainmask.mgz
- If it affects the white surface (too much/little) or If pial surface includes too little:
  - edit the wm.mgz (*if segmentation error*)
  - add control points (*if normalization error*)

Pial surf grows from white surf



Errors in pial surface placement are typically caused by underlying errors in the white surface placement, and can be corrected by interventions that fix the white surface.

Which Volumes to Edit & When…

	Non-gm in pial surf	Non-wm in white surf	wm excluded from surf & intensity = 110	wm excluded from surf & intensity < 110	Cerebellum in pial surf
brainmask.mgz	X				
brain.finalsurfs.mgz	X				X
wm.mgz		X	X		
add control points				X	

FreeSurfer Remembers!

- When edits are made, the changes are saved in a way that indicates manual changes were made (e.g. voxels that are erased are set to 1, not 0, so we can detect them)
- Re-running with a new version preserves these changes.
- To rerun without edits, use –clean flags or start from scratch

---

Summary

- Hard Errors (recon-all.log file)
- Soft Errors – surfaces not accurate
- Change volumes, regenerate surfaces
  - Manual touch ups (erase, fill, clone, control points)
  - Volumes: brainmask.mgz, wm.mgz
- Skull strip: too much, not enough
- Segmentation: WM classified as non-WM, or reverse
- FreeSurfer keeps track of edits
- Look at all 3 views and scroll back and forth a few slices

- Should take less than 30 min (or even 15min)
- If you don't know, leave it alone

Troubleshooting – Advice (Bruce)

- Always look at the data in multiple views and scroll back and forth a few slices – 3D structure is difficult to discern!
- If large regions of white matter are significantly darker than 110 (the target white matter intensity for normalization) then try adding control points, but make sure they are in the interior of the white matter.
- If the ?h.orig surface misses white matter that is accurately labeled in the wm.mgz or extends into regions where there is no wm in the wm.mgz, then there is an incorrectly fixed topological defect.
- Even one or two missing voxels can cause large-scale defects, so very minor editing (e.g. filling in white matter voxels that are holes, or erasing handles) may fix the problem.
- Don't edit too much! This will reduce reliability and is almost never needed. Usually this means you need to start over as you've done something wrong (e.g. put control points in the wrong place).

Troubleshooting – Advice (Allison)

FLOW

AMBIGUITY

CONSISTENCY

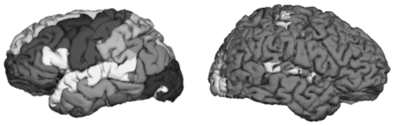
- Edit consistently within and across subjects.

SPEED

- You will get faster with time; certain sections go faster.

- freesurfer.net

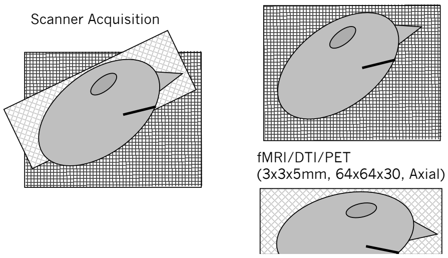
Multimodal Integration



Outline

- Spatial Transformation
- Motion Correction
- Registration, Automatic and Manual
- MultiModal Integration
  - DTI Integration
  - fMRI Integration
  - Viewing on Volume and Surface
  - ROI analyses
  - Surface-based group analysis

Spatial Transformations

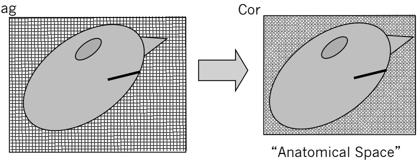


Scanner Acquisition

Anatomical (1x1x1.1mm,
256x256x128, Sag)

fMRI/DTI/PET
(3x3x5mm, 64x64x30, Axial)

Spatial Transformations

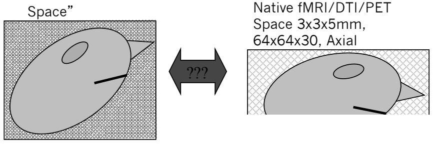


Native Anatomical Space
1x1x1.1mm, 256x256x128,
Sag

Conformed Anatomical Space
1x1x1mm, 256x256x256,
Cor

"Anatomical Space"
orig.mgz
Surfaces
Parcellations
Segmentations

Spatial Transformations



"Anatomical
Space"

Native fMRI/DTI/PET
Space 3x3x5mm,
64x64x30, Axial

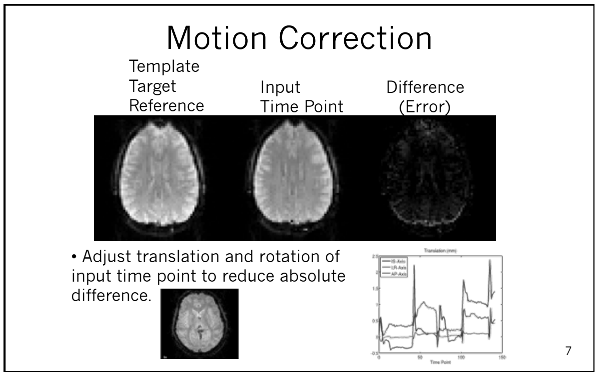
Conformed Anatomical Space
1x1x1mm, 256x256x256,
Cor

---

fMRI/DTI/PET

Have Multiple Frames/Time Points

Movement!



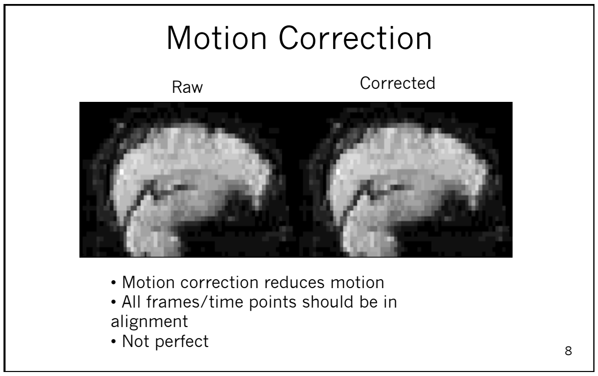
Motion Correction

Template
Target
Reference

Input
Time Point

Difference
(Error)

- Adjust translation and rotation of input time point to reduce absolute difference.

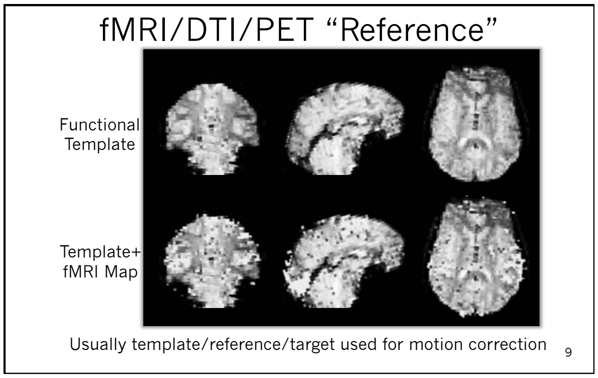


Motion Correction

Raw

Corrected

- Motion correction reduces motion
- All frames/time points should be in alignment
- Not perfect

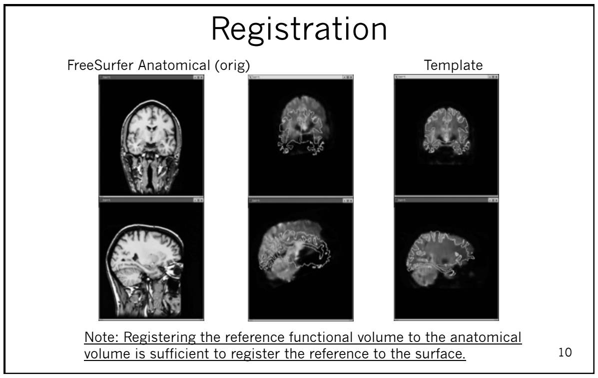


fMRI/DTI/PET “Reference”

Functional
Template

Template+
fMRI Map

Usually template/reference/target used for motion correction

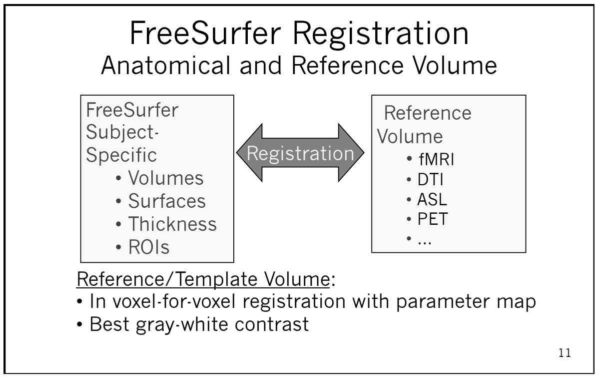


Registration

FreeSurfer Anatomical (orig)

Template

Note: Registering the reference functional volume to the anatomical volume is sufficient to register the reference to the surface.



FreeSurfer Registration

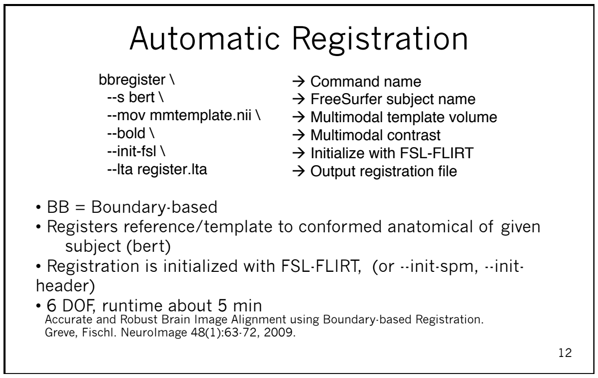
Anatomical and Reference Volume

FreeSurfer Subject-Specific
- Volumes
- Surfaces
- Thickness
- ROIs

Registration

Reference Volume
- fMRI
- DTI
- ASL
- PET
- …

Reference/Template Volume:
- In voxel-for-voxel registration with parameter map
- Best gray-white contrast



Automatic Registration

```
bbregister \                   → Command name
  --s bert \                   → FreeSurfer subject name
  --mov mmtemplate.nii \       → Multimodal template volume
  --bold \                     → Multimodal contrast
  --init-fsl \                 → Initialize with FSL-FLIRT
  --lta register.lta           → Output registration file
```

- BB = Boundary-based
- Registers reference/template to conformed anatomical of given subject (bert)
- Registration is initialized with FSL-FLIRT, (or --init-spm, --init-header)
- 6 DOF, runtime about 5 min

Accurate and Robust Brain Image Alignment using Boundary-based Registration.
Greve, Fischl. NeuroImage 48(1):63-72, 2009.

Manual Registration

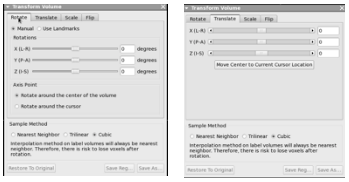
```
freeview -v template.nii \
          $SUBJECTS_DIR/fbirn-anat-101.v4/mri/orig.mgz:visible=0 \
     -f  $SUBJECTS_DIR/fbirn-anat-101.v4/surf/lh.white:edgecolor=green \ $SUBJECTS_DIR/
          fbirn-anat-101.v4/surf/rh.white:edgecolor=green \
     -viewport coronal
```

- Turn the orig volume on/off or change opacity of top volume to see current quality of alignment
- Select volume to move, then "Tools" and "Transform Volume"
- Explore the Translate and Rotate tabs
- To restart the process, use "Restore to Original"
- Use the "Save Reg" button to save the registration matrix
- Use the "Save As" button to save the resampled volume in the new coordinate system (will also save a registration file automatically)
- Default registration matrix file format: .lta

freeview --help

Manual Registration

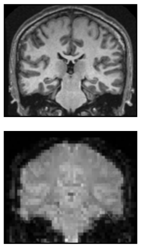
- Visually inspect registration
- Manually edit registration (6 DOF)
- cf Manual Talairach registration
- Green line is white surface



X (L-R) 0 degrees
Y (P-A) 0 degrees
Z (I-S) 0 degrees

X (L-R) 0
Y (P-A) 0
Z (I-S) 0

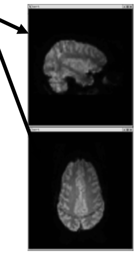
Interpolation method on label volumes will always be nearest neighbor. Therefore, there is risk to lose voxels after rotation.

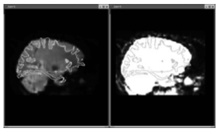


freeview --help

Manual Registration

- Rigid = 6 DOF = No stretching
- Use CSF to get a sense of where the folds are
- Avoid using B0 distortion regions
- Avoid using ventricles
- Warning about "edge" of the brain
- Same Subject, Left-Right Flips





FreeSurfer Registration Matrix

- Simple text file
- Default format: **.lta** (still supporting .dat)
- 4x4 Matrix to encode the transformation
- As many as 12 DOF (usually 6 = rigid)
- Also source / target file information
- Coordinate system not easy to explain

LTA Transform File

```
type      = 0
nxforms   = 1
mean      = 0.0000 0.0000 0.0000
sigma     = 1.0000
1 4 4
9.999998807907104e-01 6.519258022308350e-09 3.725290298461914e-09 8.798942565917969e-01
3.725290298461914e-09 1.000000000000000e+00 0.000000000000000e+00 -6.664600372314453e+00
-9.313225746154785e-10 0.000000000000000e+00 9.999998807907104e-01 6.571158409118652e+00
0.000000000000000e+00 0.000000000000000e+00 0.000000000000000e+00 1.000000000000000e+00
src volume info
valid = 1  # volume info valid
filename = template.nii
volume = 64 64 35
voxelsize = 3.437500000000000e+00 3.437499761581421e+00 4.000000000000000e+00
xras   = -9.972996711730957e-01 -7.120382040739059e-02 1.798351481556892e-02
yras   = 6.254287064075470e-02 -9.518167972564697e-01 -3.002218902111053e-01
zras   = 3.849399834871292e-02 -2.982859909534454e-01 9.537000060081482e-01
cras   = 1.612358093261719e+00 1.616348266601562e+00 4.727973937988281e+00
dst volume info
valid = 1  # volume info valid
filename = template.nii
volume = 64 64 35
voxelsize = 3.437500000000000e+00 3.437499761581421e+00 4.000000000000000e+00
xras   = -9.972996711730957e-01 -7.120382040739059e-02 1.798351481556892e-02
yras   = 6.254287064075470e-02 -9.518167972564697e-01 -3.002218902111053e-01
zras   = 3.849399834871292e-02 -2.982859909534454e-01 9.537000060081482e-01
cras   = 1.612358093261719e+00 1.616348266601562e+00 4.727973937988281e+00
```

LTA Transform File

```
type      = 0                                                                          → Type of transform (vox or RAS)
nxforms   = 1                                                                          → Number of linear transforms
mean      = 0.0000 0.0000 0.0000                                                       → Center of transform
sigma     = 1.0000                                                                     → Spread of transform
1 4 4                                                                                  → Matrix type, rows, cols
9.999998807907104e-01 6.519258022308350e-09 3.725290298461914e-09 8.798942565917969e-01      → Matrix
3.725290298461914e-09 1.000000000000000e+00 0.000000000000000e+00 -6.664600372314453e+00
-9.313225746154785e-10 0.000000000000000e+00 9.999998807907104e-01 6.571158409118652e+00
0.000000000000000e+00 0.000000000000000e+00 0.000000000000000e+00 1.000000000000000e+00
src volume info                                                                        → Subject volume information
valid = 1  # volume info valid                                                         → Validity bit
filename = template.nii                                                                → File name
volume = 64 64 35                                                                      → Volume size
voxelsize = 3.437500000000000e+00 3.437499761581421e+00 4.000000000000000e+00      → Voxel size
xras   = -9.972996711730957e-01 -7.120382040739059e-02 1.798351481556892e-02       → RAS info
yras   = 6.254287064075470e-02 -9.518167972564697e-01 -3.002218902111053e-01
zras   = 3.849399834871292e-02 -2.982859909534454e-01 9.537000060081482e-01
cras   = 1.612358093261719e+00 1.616348266601562e+00 4.727973937988281e+00
dst volume info                                                                        → Destination volume information
valid = 1  # volume info valid                                                         → Validity bit
filename = template.nii                                                                → File name
volume = 64 64 35                                                                      → Volume size
voxelsize = 3.437500000000000e+00 3.437499761581421e+00 4.000000000000000e+00      → Voxel size
xras   = -9.972996711730957e-01 -7.120382040739059e-02 1.798351481556892e-02       → RAS info
yras   = 6.254287064075470e-02 -9.518167972564697e-01 -3.002218902111053e-01
zras   = 3.849399834871292e-02 -2.982859909534454e-01 9.537000060081482e-01
cras   = 1.612358093261719e+00 1.616348266601562e+00 4.727973937988281e+00
```

Command-line Tools

Automatic Registration:

- bbregister --help
- fslregister --help
- spmregister --help
- reg-feat2anat --help

} FreeSurfer Scripts

Manual Registration:

- freeview --help

Transformations:

- mri_vol2surf --help
- mri_vol2vol --help
- mri_label2vol --help
- mri_surf2vol --help

A Non-Physicist’s Intro to Diffusion MRI

Dylan Tisdall

Diffusion

Diffusion

gradient

Diffusion

gradient

Diffusion

no gradient

Diffusion

opposite
gradient

Diffusion

opposite
gradient

Water molecules diffuse (move) inside of all tissues.

At 37 C, water has a diffusion rate of 3×10^{-3} mm^2/s.

We expect a displacement of about 17 μm in 50 ms

Diffusion

gradient

Diffusion

gradient

Diffusion

no gradient

Diffusion

no gradient

Diffusion

no gradient

Diffusion

opposite
gradient

Diffusion

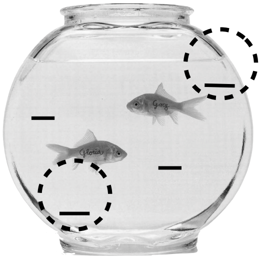
opposite
gradient

Diffusion

stationary =
re-focused

opposite
gradient

Diffusion



diffused =
not
re-focused

opposite
gradient

Diffusion

signal has cancelled out because of
diffusion parallel to the gradients

What happens with diffusion perpendicular to the gradients?

Diffusion

gradient

Diffusion

gradient

Diffusion

no gradient

Diffusion

no gradient

Diffusion

no gradient

Diffusion

opposite
gradient

Diffusion

opposite
gradient

Diffusion

stationary =
re-focused

opposite
gradient

Diffusion

diffused =
re-focused

opposite
gradient

Diffusion

signal is unaffected by
diffusion perpendicular to the gradients

Diffusion imaging uses gradients to cancel out signal in water that moves in one direction.

Diffusion imaging uses gradients to cancel out signal in water that moves in one direction.

Repeating the experiment, each time using gradient in a different direction, creates a map of how freely water diffuses in each voxel.

---

questions?

Introduction to diffusion MRI

Anastasia Yendiki

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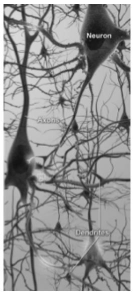
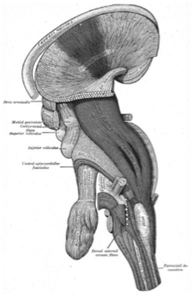
Biomedical Imaging

White-matter imaging



From the National Institute on Aging

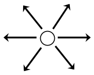
- Axons measure ~μm in width
- They group together in bundles that traverse the white matter
- We cannot image individual axons but we can image bundles with diffusion MRI
- Useful in studying neurodegenerative diseases, stroke, aging, development…



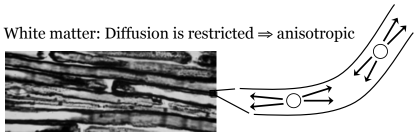
From *Gray's Anatomy: IX. Neurology*

Diffusion in brain tissue

- Differentiate between tissues based on the diffusion (random motion) of water molecules within them
- Gray matter: Diffusion is unrestricted ⇒ isotropic

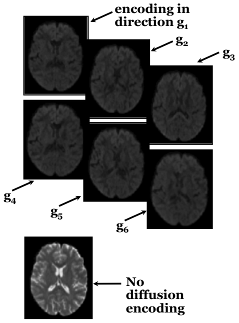


- White matter: Diffusion is restricted ⇒ anisotropic

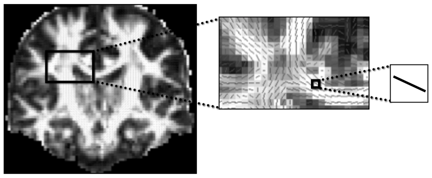


Diffusion MRI

- Magnetic resonance imaging can provide “diffusion encoding”
- Magnetic field strength is varied by gradients in different directions
- Image intensity is attenuated depending on water diffusion in each direction
- Compare with baseline images to infer on diffusion process



How to represent diffusion



- At every voxel we want to know:
    - Is this in white matter?
    - If yes, what pathway(s) is it part of?
        - What is the orientation of diffusion?
        - What is the magnitude of diffusion?
- A grayscale image cannot capture all this!

Tensors

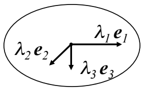
- One way to express the notion of direction is a tensor D
- A tensor is a 3x3 symmetric, positive-definite matrix:

$$D = \begin{bmatrix} d_{11} & d_{12} & d_{13} \\ d_{12} & d_{22} & d_{23} \\ d_{13} & d_{23} & d_{33} \end{bmatrix}$$

- D is symmetric 3x3 ⇒ It has 6 unique elements
- Suffices to estimate the upper (lower) triangular part

Eigenvalues & eigenvectors

- The matrix D is positive-definite ⇒
  - $\lambda_1, \lambda_2, \lambda_3 > 0.$
  - $\boldsymbol{e}_1, \boldsymbol{e}_2, \boldsymbol{e}_3.$



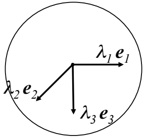
$$D = \underbrace{\lambda_1}_{\text{eigenvalue}} \underbrace{\boldsymbol{e}_1}_{\text{eigenvector}} \boldsymbol{e}_1' + \lambda_2 \boldsymbol{e}_2 \boldsymbol{e}_2' + \lambda_3 \boldsymbol{e}_3 \boldsymbol{e}_3'$$

$$\boldsymbol{e}_i = \begin{bmatrix} e_{ix} \\ e_{iy} \\ e_{iz} \end{bmatrix}$$

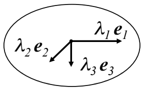
Physical interpretation

- Eigenvectors express diffusion direction
- Eigenvalues express diffusion magnitude

Isotropic diffusion:
$\lambda_1 \approx \lambda_2 \approx \lambda_3$



Anisotropic diffusion:
$\lambda_1 >> \lambda_2 \approx \lambda_3$

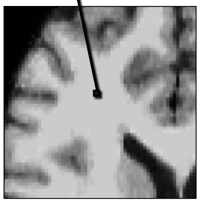


- One such ellipsoid at each voxel: Likelihood of water molecule displacements at that voxel

Diffusion tensor imaging (DTI)

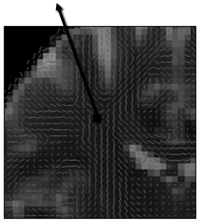
Image:

An intensity value at each voxel



Tensor map:

A tensor at each voxel

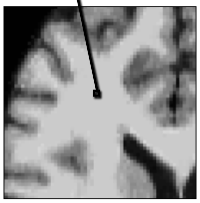


Direction of eigenvector corresponding to greatest eigenvalue

Diffusion tensor imaging (DTI)

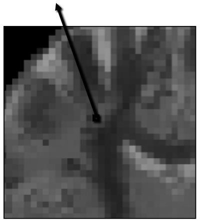
Image:

An intensity value at each voxel



Tensor map:

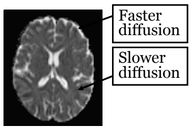
A tensor at each voxel



Direction of eigenvector corresponding to greatest eigenvalue

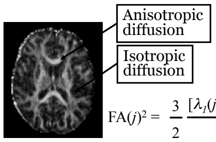
Red: L-R, Green: A-P, Blue: I-S

Summary measures



- Mean diffusivity (MD): Mean of the 3 eigenvalues

$\mathrm{MD}(j) = [\lambda_1(j)+\lambda_2(j)+\lambda_3(j)]/3$



- Fractional anisotropy (FA): Variance of the 3 eigenvalues, normalized so that $0 \leq (\mathrm{FA}) \leq 1$

$$\mathrm{FA}(j)^2 = \frac{3}{2} \frac{[\lambda_1(j)-\mathrm{MD}(j)]^2 + [\lambda_2(j)-\mathrm{MD}(j)]^2 + [\lambda_3(j)-\mathrm{MD}(j)]^2}{\lambda_1(j)^2 + \lambda_2(j)^2 + \lambda_3(j)^2}$$

More summary measures

- Axial diffusivity: Greatest of the 3 eigenvalues

  $\mathrm{AD}(j) = \lambda_1(j)$

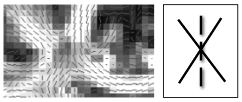
- Radial diffusivity: Average of 2 lesser eigenvalues

  $\mathrm{RD}(j) = [\lambda_2(j) + \lambda_3(j)]/2$

- Inter-voxel coherence: Average angle b/w the major eigenvector at some voxel and the major eigenvector at the voxels around it

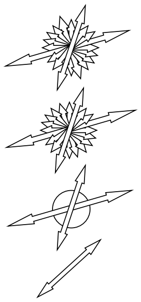
Beyond the tensor

- The tensor is an imperfect model: What if more than one major diffusion direction in the same voxel?



- High angular resolution diffusion imaging (HARDI): More complex models to capture more complex microarchitecture
  - [Tuch' 02]
  - [Frank' 02, Özarslan' 03]
  - [Behrens' 03]
  - [Tuch' 04]
  - [Wedeen' 05]

Models of diffusion



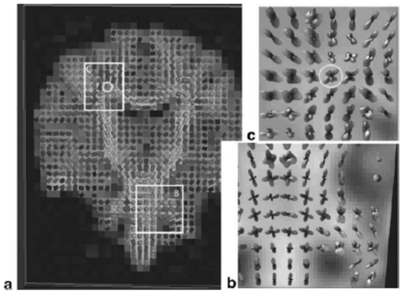
Diffusion spectrum (DSI):
Full distribution of orientation and magnitude

Orientation distribution function (Q-ball):
No magnitude info, only orientation

Ball-and-stick:
Orientation and magnitude for up to N anisotropic compartments

Tensor (DTI):
Single orientation and magnitude

Example: DTI vs. DSI



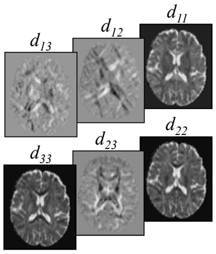
From Wedeen *et al.*, Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging, MRM 2005

Data acquisition

- Remember: A tensor has six unique parameters

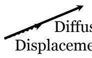
$$D = \begin{bmatrix} d_{11} \; d_{12} \; d_{13} \\ d_{12} \; d_{22} \; d_{23} \\ d_{13} \; d_{23} \; d_{33} \end{bmatrix}$$

- To estimate six parameters at each voxel, must acquire at least six diffusion-weighted images
- HARDI models have more parameters per voxel, so more images must be acquired



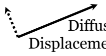
Choice 1: Gradient directions

- True diffusion direction || Applied gradient direction
  ⇒ Maximum attenuation



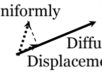
Diffusion-encoding gradient ***g***
Displacement detected

- True diffusion direction ⊥ Applied gradient direction
  ⇒ No attenuation



Diffusion-encoding gradient ***g***
Displacement not detected

- To capture all diffusion directions well, gradient directions should cover 3D space uniformly



Diffusion-encoding gradient ***g***
Displacement partly detected

How many directions?

- Acquiring data with more gradient directions leads to:
  +
  – ⇒
  susceptible to artifacts due to motion, respiration, etc.

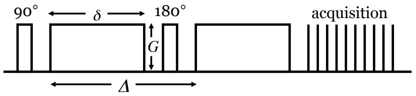
- DTI:
  - Six directions is the minimum
  - Usually a few 10' s of directions
  - Diminishing returns after a certain number [Jones, 2004]
- HARDI/DSI:
  - Usually a few 100' s of directions

Choice 2: The b-value

- The b-value depends on acquisition parameters:

$$b = \gamma\ G^2\ \delta^2\ (\Delta - \delta/3)$$

  - γ the gyromagnetic ratio
  - G the strength of the diffusion-encoding gradient
  - δ the duration of each diffusion-encoding pulse
  - Δ the interval b/w diffusion-encoding pulses



How high b-value?

- Increasing the b-value leads to:
  - \+ Increased contrast b/w areas of higher and lower diffusivity in principle
  - – Decreased signal-to-noise ratio ⇒ Less reliable estimation of diffusion measures in practice

- DTI: b ~ 1000 sec/mm^2
- HARDI/DSI: b ~ 10,000 sec/mm^2

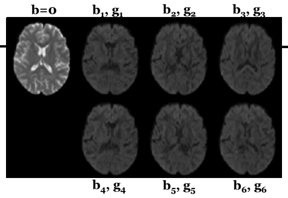
- Data can be acquired at multiple b-values for trade-off
- Repeat acquisition and average to increase signal-to-noise ratio

---

Looking at the data

A diffusion data set consists of:

- A set of non-diffusion-weighted a.k.a "baseline" a.k.a. "low-b" images (b-value = 0)
- A set of diffusion-weighted (DW) images acquired with different gradient directions g_1, g_2, … and b-value >0
- The diffusion-weighted images have lower intensity values



Baseline image

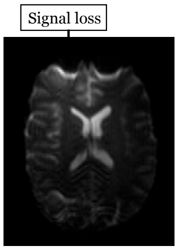
Diffusion-weighted images

Distortions: Field inhomogeneities

- Causes:
  - – Scanner-dependent (imperfections of main magnetic field)
  - – Subject-dependent (changes in magnetic susceptibility in tissue/air interfaces)

- Results:
  - – Signal loss in interface areas
  - – Geometric distortions (warping) of the entire image

Signal loss



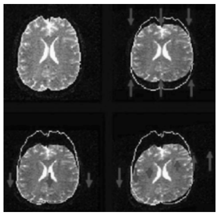
Distortions: Eddy currents

- Cause: Fast switching of diffusion-encoding gradients induces eddy currents in conducting components

- Eddy currents lead to residual gradients that shift the diffusion gradients

- The shifts are direction-dependent, *i.e.,* different for each DW image

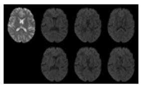
- Result: Geometric distortions



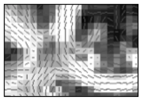
From Le Bihan *et al.*, Artifacts and pitfalls in diffusion MRI, JMRI 2006

Data analysis steps

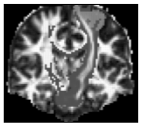
- Pre-process images to reduce distortions
  - Either register distorted DW images to an undistorted (non-DW) image
  - Or use information on distortions from separate scans (field map, residual gradients)

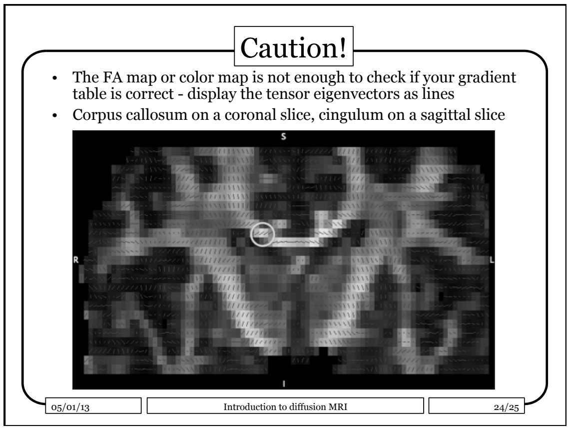


- Fit a diffusion model at every voxel
  - DTI, DSI, Q-ball, …



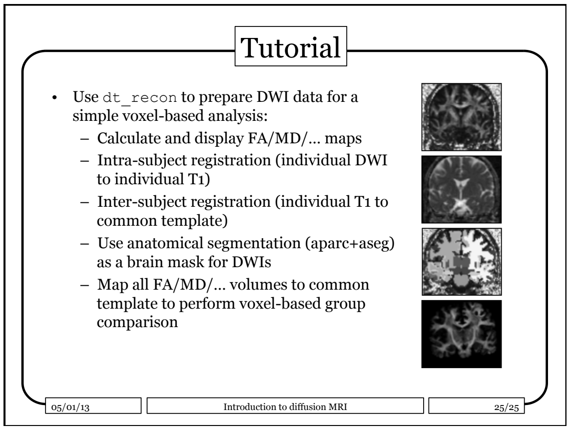
- Do tractography to reconstruct pathways and/or
- Compute measures of anisotropy/diffusivity and compare them between populations
  - Voxel-based, ROI-based, or tract-based statistical analysis





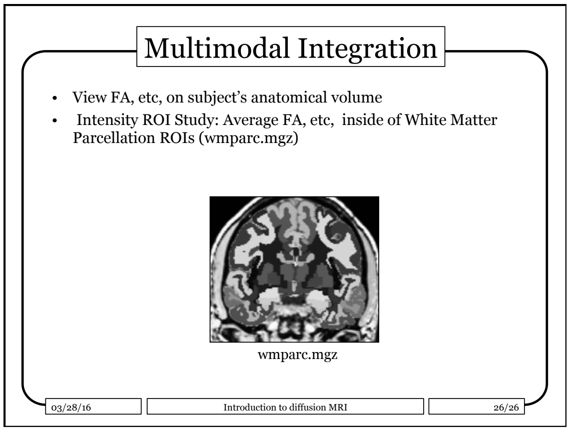
Caution!

- The FA map or color map is not enough to check if your gradient table is correct - display the tensor eigenvectors as lines
- Corpus callosum on a coronal slice, cingulum on a sagittal slice



Tutorial

- Use `dt_recon` to prepare DWI data for a simple voxel-based analysis:
  - Calculate and display FA/MD/… maps
  - Intra-subject registration (individual DWI to individual T1)
  - Inter-subject registration (individual T1 to common template)
  - Use anatomical segmentation (aparc+aseg) as a brain mask for DWIs
  - Map all FA/MD/… volumes to common template to perform voxel-based group comparison



Multimodal Integration

- View FA, etc, on subject's anatomical volume
- Intensity ROI Study: Average FA, etc, inside of White Matter Parcellation ROIs (wmparc.mgz)

wmparc.mgz

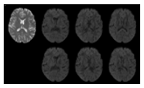
TRACULA

Anastasia Yendiki

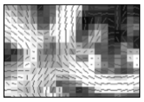
HMS/MGH/MIT Athinoula A. Martinos Center for Biomedical Imaging

Data analysis steps

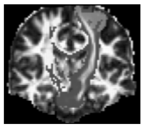
- Pre-process images to reduce distortions
  - Either register distorted DW images to an undistorted (non-DW) image
  - Or use information on distortions from separate scans (field map, residual gradients)



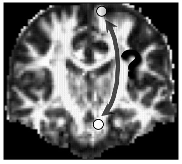
- Fit a diffusion model at every voxel
  - DTI, DSI, Q-ball, …



- Do tractography to reconstruct pathways and/or
- Compute measures of anisotropy/diffusivity and compare them between populations
  - Voxel-based, ROI-based, or tract-based statistical analysis



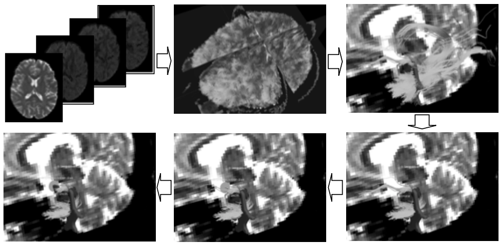
Tractography studies



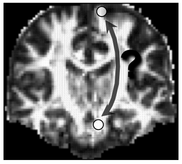
- Exploratory tractography:
  - Example: *Show me all regions that the motor cortex is connected to.*
  - Seed region can be anatomically defined (motor cortex) or functionally defined (region activated in an fMRI finger-tapping task)
- Tractography of known pathways:
  - Example: *Show me the corticospinal tract.*
  - Use prior anatomical knowledge of the pathway's terminations and trajectory (connects motor cortex and brainstem through capsule)

Tractography takes time

- Get whole-brain tract solutions, edit manually
- Use knowledge of anatomy to isolate specific pathways



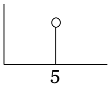
Tractography methods

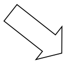


- Use local diffusion orientation at each voxel to determine pathway between distant brain regions
- Local orientation comes from diffusion model fit (tensor, ball-and-stick, etc.)
- Deterministic vs. probabilistic tractography:
  - Deterministic assumes a single orientation at each voxel
  - Probabilistic assumes a distribution of orientations
- Local vs. global tractography:
  - Local fits the pathway to the data one step at a time
  - Global fits the entire pathway at once

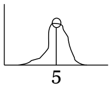
Deterministic vs. probabilistic

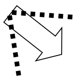
- Deterministic methods give you an estimate of model parameters



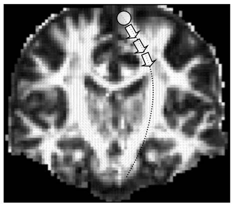


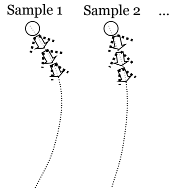
- Probabilistic methods give you the uncertainty (probability distribution) of the estimate





Deterministic vs. probabilistic

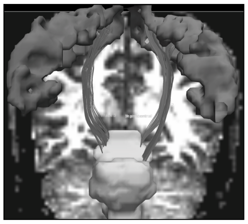




Deterministic tractography:
One streamline per seed voxel

Probabilistic tractography:
Multiple streamline samples per seed voxel (drawn from probability distribution)

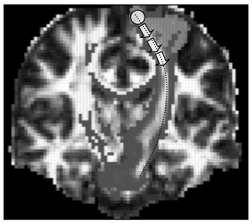
Deterministic vs. probabilistic

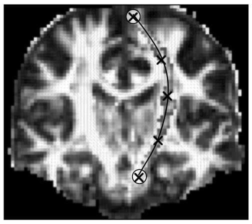


Deterministic tractography:
One streamline per seed voxel

Probabilistic tractography:
A probability distribution
(sum of all streamline samples from all seed voxels)

Local vs. global



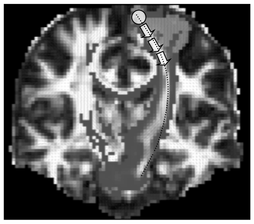


Local tractography:
Fits pathway step-by-step, using local diffusion orientation at each step

Global tractography:
Fits the entire pathway, using diffusion orientation at all voxels along pathway length

---

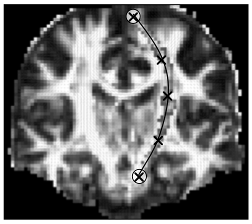
Local tractography



- Best suited for exploratory study of connections
- All connections from a seed region, not constrained to a specific target region
- How do we isolate a specific white-matter pathway?
  - Thresholding?
  - Intermediate masks?
- Non-dominant connections are hard to reconstruct
- Results are not symmetric between “seed” and “target” regions
- Sensitive to areas of high local uncertainty in orientation (*e.g.,* pathway crossings), errors propagate from those areas

---

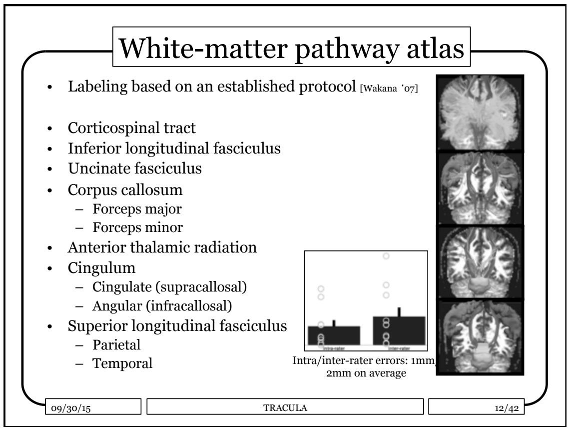
Global tractography



- Best suited for reconstruction of known white-matter pathways
- Constrained to connection of two specific end regions
- Not sensitive to areas of high local uncertainty in orientation, integrates over entire pathway
- Symmetric between “seed” and “target” regions
- Need to search through a large solution space of all possible connections between two regions:
  - Computationally expensive
  - Sensitive to initialization

TRACULA

- TRActs Constrained by UnderLying Anatomy
- Global probabilistic tractography with prior information on tract anatomy from training subjects
- Learn from training subjects which anatomical regions each pathway typically goes through/next to
- Constrain pathway in new subject based on this prior anatomical knowledge
- Reconstruct 18 major white-matter pathways
  - No manual intervention in new subjects
  - Robustness with respect to pathway initialization
  - Anatomically plausible solutions
- Ad-hoc anatomical constraints are often used by other methods: constraints on path bending angle or length, WM masks, …

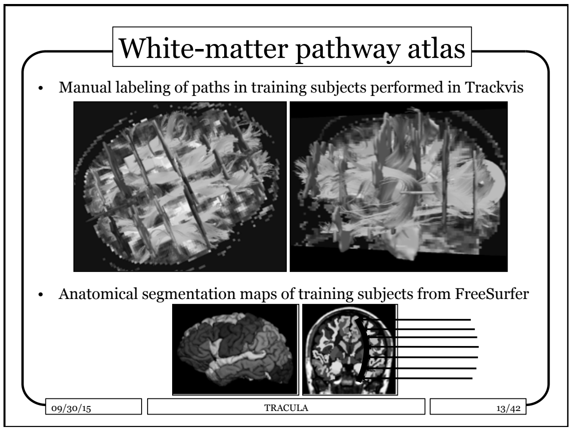


White-matter pathway atlas

- Labeling based on an established protocol [Wakana '07]

- Corticospinal tract
- Inferior longitudinal fasciculus
- Uncinate fasciculus
- Corpus callosum
  - Forceps major
  - Forceps minor
- Anterior thalamic radiation
- Cingulum
  - Cingulate (supracallosal)
  - Angular (infracallosal)
- Superior longitudinal fasciculus
  - Parietal
  - Temporal

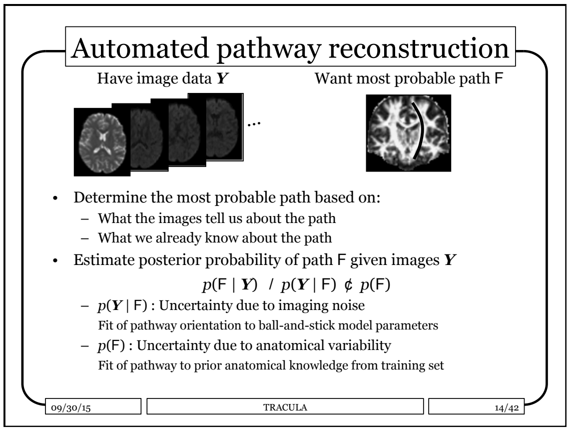
Intra/inter-rater errors: 1mm/
2mm on average



White-matter pathway atlas

- Manual labeling of paths in training subjects performed in Trackvis
- Anatomical segmentation maps of training subjects from FreeSurfer

---



Automated pathway reconstruction

Have image data $\boldsymbol{Y}$ Want most probable path F

- Determine the most probable path based on:
  - What the images tell us about the path
  - What we already know about the path
- Estimate posterior probability of path F given images $\boldsymbol{Y}$

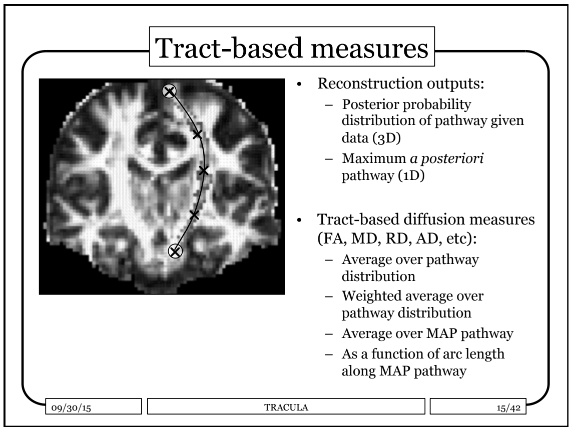
$$p(\mathsf{F} \mid \boldsymbol{Y}) \;\; / \;\; p(\boldsymbol{Y} \mid \mathsf{F}) \;\; \text{¢} \;\; p(\mathsf{F})$$

  - $p(\boldsymbol{Y} \mid \mathsf{F})$: Uncertainty due to imaging noise

    Fit of pathway orientation to ball-and-stick model parameters
  - $p(\mathsf{F})$: Uncertainty due to anatomical variability

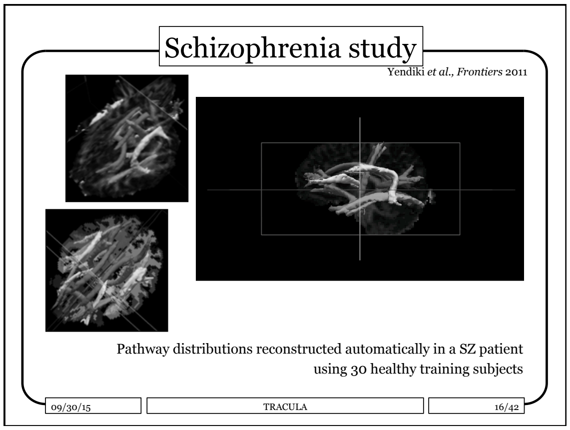
    Fit of pathway to prior anatomical knowledge from training set

---



Tract-based measures

- Reconstruction outputs:
  - Posterior probability distribution of pathway given data (3D)
  - Maximum *a posteriori* pathway (1D)
- Tract-based diffusion measures (FA, MD, RD, AD, etc):
  - Average over pathway distribution
  - Weighted average over pathway distribution
  - Average over MAP pathway
  - As a function of arc length along MAP pathway



Schizophrenia study

Yendiki *et al., Frontiers* 2011

Pathway distributions reconstructed automatically in a SZ patient using 30 healthy training subjects

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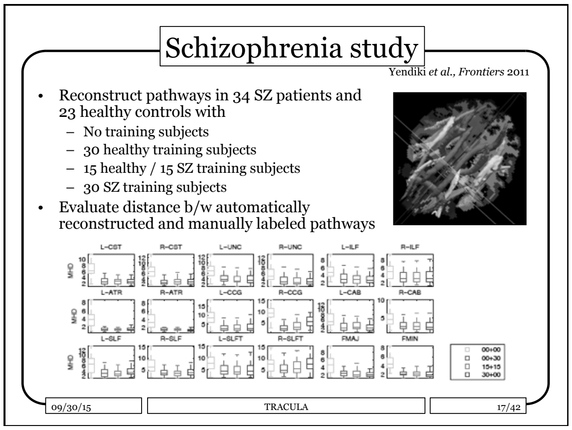


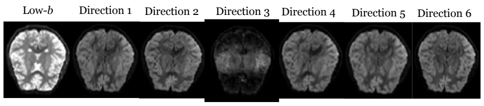
Schizophrenia study

Yendiki *et al., Frontiers* 2011

- Reconstruct pathways in 34 SZ patients and 23 healthy controls with
  - No training subjects
  - 30 healthy training subjects
  - 15 healthy / 15 SZ training subjects
  - 30 SZ training subjects
- Evaluate distance b/w automatically reconstructed and manually labeled pathways

Head motion in diffusion MRI

- Head motion during a dMRI scan can lead to:
  - Misalignment between consecutive DWI volumes in the series
  - Attenuation in the intensities of a single DWI volume/slice, if the motion occurred during the diffusion-encoding gradient pulse
  - The former can be corrected with rigid registration, *the latter can't*



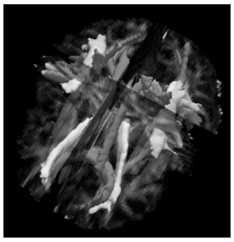
- Conventional EPI sequences for dMRI ignore the problem
  - If motion in several directions ⇒ underestimation of anisotropy
  - False positives in group studies where one group moves more
  - Effects more severe when higher *b*-values, more directions acquired

---

Motion in a dMRI group study

Yendiki *et al., Neuroimage* 2014

- 57 children with autism spectrum disorder (ASD)
- 73 typically developing children (TD)
- Ages 5-12
- 195 total scans (some retest)
- DWI: 3T, 2mm isotropic, 30 directions, b=700 s/mm^2
- Translation, rotation, intensity drop-out due to motion assessed
- Outlier data sets excluded
- Pathways reconstructed automatically with TRACULA

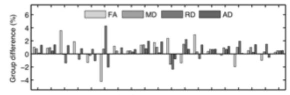


Data courtesy of Dr. Nancy Kanwisher
and Ellison autism study

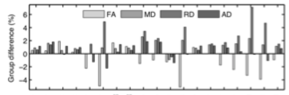
ASD vs. TD

Yendiki *et al., Neuroimage* 2014

Differences in dMRI measures between groups with low differences in head motion



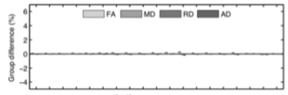
Differences in dMRI measures between groups with high differences in head motion



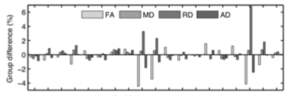
TD vs. TD

Yendiki *et al., Neuroimage* 2014

Differences in dMRI measures between groups with low differences in head motion



Differences in dMRI measures between groups with high differences in head motion



Head motion, in summary

Yendiki *et al., Neuroimage* 2014

- Differences in head motion between groups can induce spurious group differences in diffusivity and anisotropy
- General trend: Head motion↑ ⇒ RD↑, AD↓, MD –, FA↓
- This is *after* registration-based motion correction
- Match motion between groups and/or use a motion score as a nuisance regressor
- Note that all this will address *false positives,* but not *false negatives* due to head motion in the data
- Methods for tackling the problem during data acquisition are needed

---

TRACULA usage

- All processing options are defined in a configuration file, `dmrirc`
- Step 1: Pre-processing (distortion compensation, registration, etc.)
  `trac-all -prep -c dmrirc`
- Step 2: Fitting of ball-and-stick model (FSL's bedpostx)
  `trac-all -bedp -c dmrirc`
- Step 3: Reconstruct pathways
  `trac-all -path -c dmrirc`

Configuration file

- Example configuration file:
  `$FREESURFER_HOME/bin/dmrirc.example`
- The simplest configuration file possible, using all default options and only defining inputs:

```
setenv SUBJECTS_DIR /path/to/fs/output/directory
set subjlist = (subjA subjB …)
set dcmlist = (/path/to/A/1.dcm /path/to/B/011-1.dcm …)
set bvecfile = /path/to/bvecs.txt
set bvalfile = /path/to/bvals.txt
```

- Same gradient vectors and b-values assumed for all scans
- Can specify trac-all output directory different from recon-all `$SUBJECTS_DIR`:

```
set dtroot = /path/to/tracula/output/directory
```

Pre-processing

```
trac-all -prep -c dmrirc
```

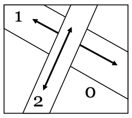
- Includes the following steps:
  - Image corrections: `-corr`
  - NEW: Quality assessment (motion scores): `-qa`
  - Intra-subject registration (DWI to T1) : `-intra`
  - Inter-subject registration (T1 to template) : `-inter`
  - Anatomical masks and labels : `-mask`
  - Tensor fit : `-tensor`
  - Anatomical priors : `-prior`
- Can do some of the steps only (assuming previous steps have been done):
  - `trac-all -corr -qa -c dmrirc`
- Or exclude some of the steps (assuming they have been done previously):
  - `trac-all -prep -nocorr -noqa -c dmrirc`

Ball-and-stick model fit

```
trac-all -bedp -c dmrirc
```

- This step simply runs FSL bedpostX to fit the ball-and-stick model of diffusion to every voxel in the brain mask
- This can take a while, but it's possible to run every slice in parallel
- To specify the maximum number of anisotropic compartments per voxel (default: 2)

```
set nstick = 3
```



Pathway reconstruction

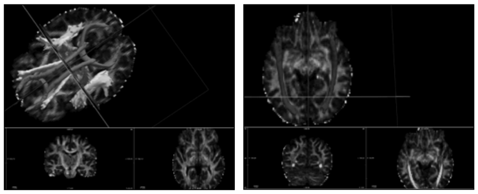
```
trac-all -path -c dmrirc
```

- Reconstruct the 18 pathways (or a subset) using a random sampling algorithm:
- Pick an initial guess for the path from the training subjects in the atlas (the only step that requires decent alignment between individual and atlas!)
- At every iteration, perturb control points of path and compute its fit to diffusion data and to anatomical priors from atlas
- To specify number of paths to sample (default: 7500)

```
set nsample = 10000
```

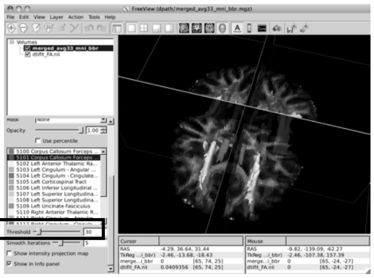
Visualization with freeview

- There is a 4D volume where all the pathway distributions that were estimated have been merged
- Opening this file in freeview will display all distributions as isosurfaces, thresholded at 20% of their maximum value.



Visualization: 3D view

```
freeview dmri/dtifit_FA.nii.gz \
      -tv dpath/merged_avg33_mni_bbr.mgz
```



Opacity 1.00

Threshold 30

Smooth iterations 5

Cursor		
RAS	-4.29, 36.64, 31.44	
TkReg ...i_bbr)	-2.46, -13.68, -18.43	
merge...i_bbr	0	[65, 74, 25]
dtifit_FA.nii	0.0409356	[65, 74, 25]

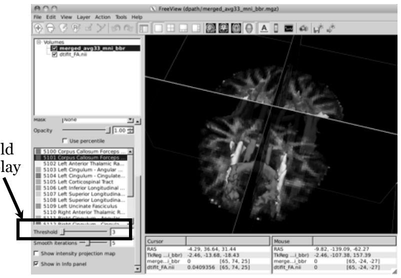
Mouse		
RAS	-9.82, -139.09, -62.27	
TkReg ...i_bbr)	-2.46, -107.38, 157.39	
merge...i_bbr	0	[65, -24, -27]
dtifit_FA.nii	0	[65, -24, -27]

Change threshold for display

Visualization: 3D view

- `freeview dmri/dtifit_FA.nii.gz \`
  `-tv dpath/merged_avg33_mni_bbr.mgz`

Change threshold for display

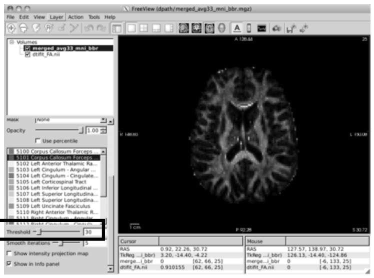


```
Cursor                                      Mouse
RAS            -4.29, 36.64, 31.44          RAS            -9.82, -139.09, -62.27
TkReg ...i_bbr) -2.46, -13.68, -18.43       TkReg ...i_bbr) -2.46, -107.38, 157.39
merge...i_bbr  0          [65, 74, 25]      merge...i_bbr  0          [65, -24, -27]
dtifit_FA.nii  0.0409356  [65, 74, 25]      dtifit_FA.nii  0          [65, -24, -27]
```

Visualization: Slice view

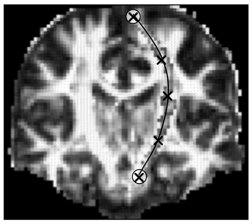
- `freeview dmri/dtifit_FA.nii.gz \`
  `-tv dpath/merged_avg33_mni_bbr.mgz`

Change threshold for display



```
Cursor                                      Mouse
RAS            0.92, 22.26, 30.72           RAS            127.57, 138.97, 30.72
TkReg ...i_bbr) 3.20, -14.40, -4.22         TkReg ...i_bbr) 126.13, -14.40, -124.86
merge...i_bbr  0          [62, 66, 25]      merge...i_bbr  0          [-6, 133, 25]
dtifit_FA.nii  0.910155   [62, 66, 25]      dtifit_FA.nii  0          [-6, 133, 25]
```

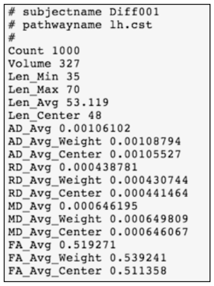
Tract-based measures



- Reconstruction outputs
  - Posterior probability distribution of pathway given data (3D):
    `paths.pd.nii.gz`
  - Maximum *a posteriori* pathway (1D):
    `path.map.nii.gz`
- Tract-based diffusion measures (FA, MD, RD, AD)
  - Averaged over the entire pathway distribution:
    `pathstats.overall.txt`
  - As a function of position along the pathway:
    `pathstats.byvoxel.txt`

Path stats (average values)

`pathstats.overall.txt`

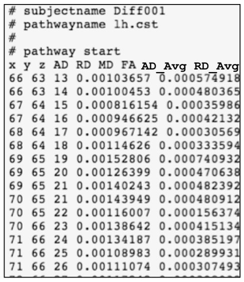


```
# subjectname Diff001
# pathwayname lh.cst
#
Count 1000
Volume 327
Len_Min 35
Len_Max 70
Len_Avg 53.119
Len_Center 48
AD_Avg 0.00106102
AD_Avg_Weight 0.00108794
AD_Avg_Center 0.00105527
RD_Avg 0.000438781
RD_Avg_Weight 0.000430744
RD_Avg_Center 0.000441464
MD_Avg 0.000646195
MD_Avg_Weight 0.000649809
MD_Avg_Center 0.000646067
FA_Avg 0.519271
FA_Avg_Weight 0.539241
FA_Avg_Center 0.511358
```

- `*_Avg`: Average values of every voxel with probability > 20% of the maximum
- `*_Avg_Weight`: Multiply value at voxel with the probability at that voxel, sum over every voxel with probability > 20% of the maximum
  - This is closest to the notion of mean/expected value
- `*_Center`: Average values only on the 1-D path with the highest probability

Path stats (values along the path)

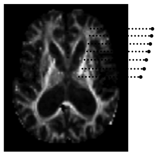
`pathstats.byvoxel.txt`



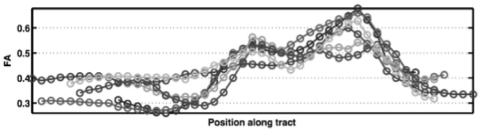
```
# subjectname Diff001
# pathwayname lh.cst
#
# pathway start
x y z AD RD MD FA AD_Avg RD_Avg
66 63 13 0.00103657 0.000574918
66 63 14 0.00100453 0.000480365
67 64 15 0.000816154 0.00035986
67 64 16 0.000946625 0.00042132
68 64 17 0.000967142 0.00030569
68 64 18 0.00114626 0.000333594
69 65 19 0.00152806 0.000740932
69 65 20 0.00126399 0.000470638
69 65 21 0.00140243 0.000482392
70 65 21 0.00143949 0.000480912
70 65 22 0.00116007 0.000156374
70 66 23 0.00138642 0.000415134
71 66 24 0.00134187 0.000385197
71 66 25 0.00108983 0.000289931
71 66 26 0.00111074 0.000307493
```

- At each position along the path
  - Value on 1-D path with the highest probability
  - `*_Avg`: Average value over nearest points from all sampled paths
- Coordinates are given in native diffusion space
- Paths from different subjects generally have different number of positions along path

Along-the-path analysis



- Compute average FA/MD/RD/AD at each cross-section of the pathway
- Plot as a function of position along the pathway
- Correspondence of points between subjects based on Euclidean distance in MNI space



New: Assemble group stats

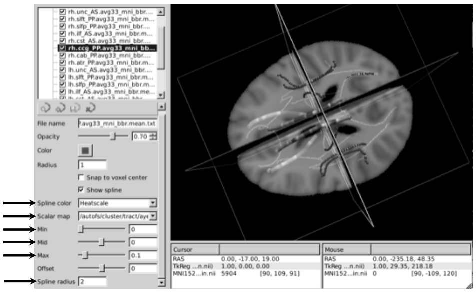
```
trac-all -stat -c dmrirc
```

- Combine files of stats along the path from multiple subjects:
  - Interpolate values of FA/MD/… at the same arc lengths for all paths
  - Find mean path for visualizing group results

- Outputs can be used for group studies on FA, MD, RD, AD along the pathway
  - One text file per pathway per measure (FA, MD, RD, AD)
  - Coordinates of mean path for visualization in freeview
  - Log file shows which subjects are outliers (shape-wise)

Example: *p*-values along each tract

- Save *p*-values in a simple text file, load it as a "scalar map"



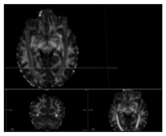
File name ?.avg33_mni_bbr.mean.txt
Opacity 0.70
Color
Radius 1
☐ Snap to voxel center
☑ Show spline
Spline color Heatscale
Scalar map /autofs/cluster/tract/ay
Min 0
Mid 0
Max 0.1
Offset 0
Spline radius 2

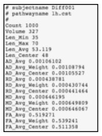
Cursor	
RAS	0.00, -17.00, 19.00
TkReg ...n.nii)	1.00, 0.00, 0.00
MNI152....in.nii	5904 [90, 109, 91]

Mouse	
RAS	0.00, -235.18, 48.35
TkReg ...n.nii)	1.00, 29.35, 218.18
MNI152....in.nii	0 [90, -109, 120]

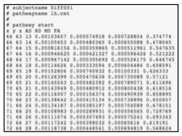
Tutorial

- How to run TRACULA and view outputs:
  - Set up configuration file (input images, gradient directions, b-values, registration method, etc.)
  - "Run" trac-all (*don't actually run it!*)
  - Look at pathways in freeview
  - Look at FA, MD, and other stats for each pathway

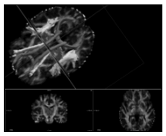




```
# subjectname Diff001
# pathwayname lh.cst
#
Count 1000
Volume 327
Len_Min 35
Len_Max 70
Len_Avg 53.119
Len_Center 48
AD_Avg 0.00106102
AD_Avg_Weight 0.00108794
AD_Avg_Center 0.00105527
RD_Avg 0.000438781
RD_Avg_Weight 0.000430744
RD_Avg_Center 0.000441464
MD_Avg 0.000646195
MD_Avg_Weight 0.000649809
MD_Avg_Center 0.000646067
FA_Avg 0.519271
FA_Avg_Weight 0.539241
FA_Avg_Center 0.511358
```

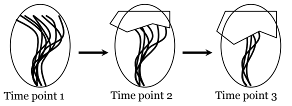


```
# subjectname Diff001
# pathwayname lh.cst
#
# pathway start
x y z AD RD MD FA
66 63 13 0.00103657 0.000574918 0.000728804 0.374774
66 63 14 0.00100453 0.000480365 0.000655088 0.478045
67 64 15 0.000816154 0.000359865 0.000511961 0.547635
67 64 16 0.000946625 0.000421327 0.000596426 0.521222
68 64 17 0.000967142 0.000305692 0.000526175 0.646745
68 64 18 0.00114626 0.000333594 0.000604484 0.658591
69 65 19 0.00152806 0.000740932 0.00100331 0.426333
69 65 20 0.00126399 0.000470638 0.000735089 0.57121
69 65 21 0.00140243 0.000482392 0.000789071 0.611696
70 65 21 0.00143949 0.000480912 0.000800438 0.618516
70 65 22 0.00116007 0.000156374 0.000490939 0.858895
70 66 23 0.00138642 0.000415134 0.000738896 0.650657
71 66 24 0.00134187 0.000385197 0.000704089 0.678151
71 66 25 0.00108983 0.000289931 0.000556565 0.729769
71 66 26 0.00111074 0.000307493 0.000575241 0.693343
72 66 27 0.00117242 0.000398032 0.00065616 0.619191
72 66 28 0.00118738 0.000448541 0.000694819 0.568624
```



New: Longitudinal tractography

- Goal: Reconstruct a white-matter pathway consistently among all time points of a subject
- Challenging to do when processing each time point independently, as if it were a cross-sectional data point

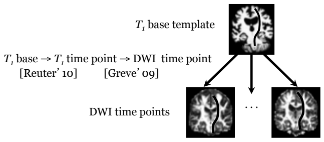


- Different parts of the pathway may be reconstructed in each time point, due to noise or white matter degeneration
  - Changes in average anisotropy/diffusivity may be underestimated
  - Point-to-point correspondence difficult to establish for along-the-path analysis of anisotropy/diffusivity

---

Longitudinal TRACULA

Yendiki *et al., ISMRM* 2014



- Reconstruct a subject's pathways simultaneously in all time points:
  - Perturb path in the space of the base template
  - Map to each time point
  - Compute likelihood of DWI data at all time points
  - Compute anatomical prior based on segmentations of all time points

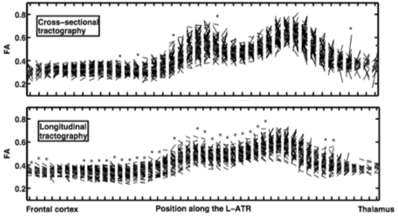
- Ensures point-to-point correspondence along path between time points
- Unbiased, treats all time points the same way

Longitudinal TRACULA: Sensitivity

Yendiki *et al., ISMRM* 2014

- Improved sensitivity to longitudinal changes in FA in Huntington's disease with longitudinal TRACULA

•: $p<0.1$ *: $p<0.05$



Longitudinal TRACULA : Usage

- Example configuration file:
  `$FREESURFER_HOME/bin/dmrirc.long.example`

- List all time points and their corresponding base templates:

```
set subjlist = (subjA-tp1 subjA-tp2 … subjB-tp1 subjB-tp2 …)
set baselist = (subjA-base subjA-base .. subjB-base subjB-base …)
```

- If `baselist` is not specified, data will be processed cross-sectionally

- The same 3 steps of trac-all must be run for either cross-sectional or longitudinal stream (the only difference is in the configuration file)

Basics of fMRI Analysis: Preprocessing, First-Level Analysis, and Group Analysis

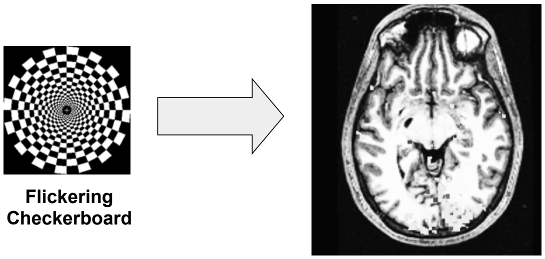
MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Overview

- Neuroanatomy 101 and fMRI Contrast Mechanism
- Preprocessing
- Hemodynamic Response
- "Univariate" GLM Analysis
- Hypothesis Testing
- Group Analysis

Visual Activation Paradigm

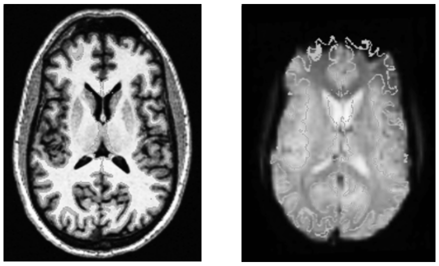


Flickering Checkerboard

Visual, Auditory, Motor, Tactile, Pain, Perceptual, Recognition, Memory, Emotion, Reward/Punishment, Olfactory, Taste, Gastral, Gambling, Economic, Acupuncture, Meditation, The Pepsi Challenge, …

- Scientific
- Clinical
- Pharmaceutical

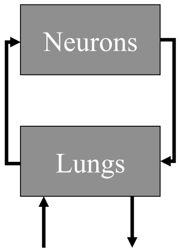
Magnetic Resonance Imaging



T1-weighted Contrast

BOLD-weighted Contrast

Blood Oxygen Level Dependent (BOLD)



Oxygenated Hemoglobin (DiaMagnetic)

Neurons

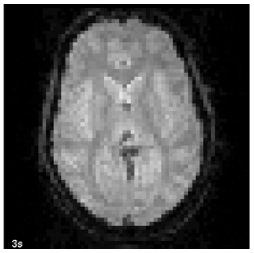
Lungs

Deoxygenated Hemoglobin (ParaMagnetic)

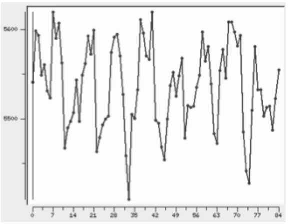
Contrast Agent

Oxygen CO_2

4D Volume

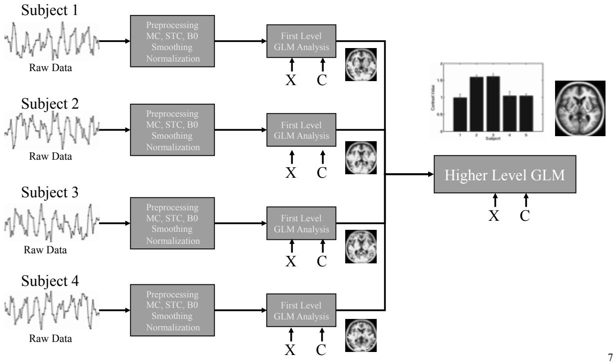


64×64×35



85×1

fMRI Analysis Overview



Preprocessing

- Assures that assumptions of the analysis are met
  - Time course comes from a single location
  - Uniformly spaced in time
  - Spatial “smoothness”
- vs Analysis – separating signal from noise

Preprocessing

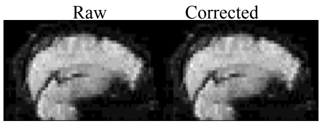
- Start with a 4D data set
1. Motion Correction
2. Slice-Timing Correction
3. B_0 Distortion Correction
4. Spatial Normalization
5. Spatial Smoothing
- End with a 4D data set

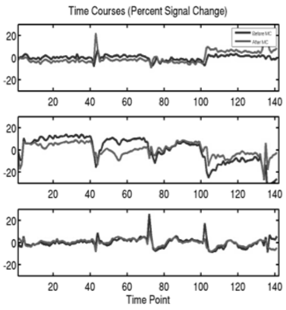
- Can be done in other orders
- Not everything is always done

Motion

- Analysis assumes that time course represents a value from a single location
- Subjects move
- Shifts can cause noise, uncertainty
  - Edge of the brain and tissue boundaries

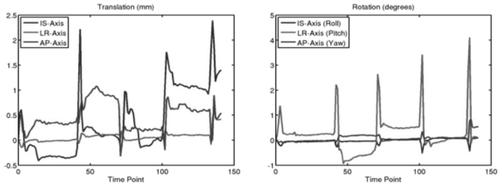
Motion and Motion Correction





- Motion correction reduces motion
- Not perfect

Motion Correction



- Motion correction parameters
- Six for each time point
- Sometimes used as nuisance regressors
- How much motion is too much?

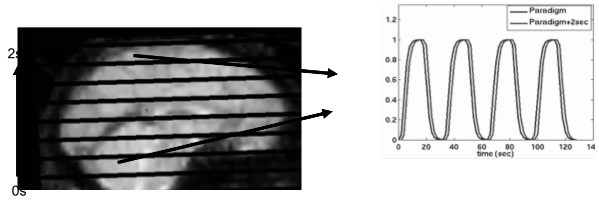
Slice Timing

Ascending
Interleaved

- Volume not acquired all at one time
- Acquired slice-by-slice
- Each slice has a different delay

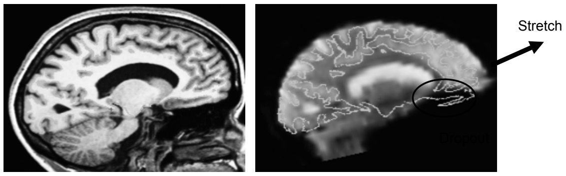
Effect of Slice Delay on Time Course

- Volume = 30 slices
- TR = 2 sec
- Time for each slice = 2/30 = 66.7 ms



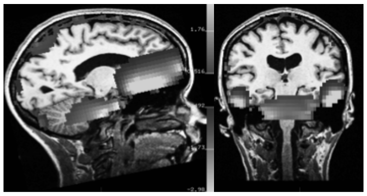
Can be corrected, but you must know the slice timing!

B_0 Distortion



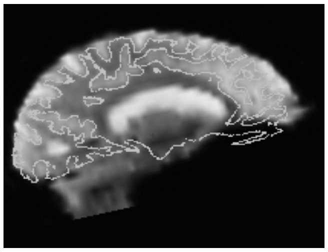
- Metric (stretching or compressing)
- Intensity Dropout
- A result of a long readout needed to get an entire slice in a single shot.
- Caused by B_0 Inhomogeneity

B0 Map: Voxel Shift Map



- Units are voxels (3.5 mm)
- Shift is in-plane
- Blue = P→A, Red A→P
- Regions affected near air/tissue boundaries (eg, sinuses)

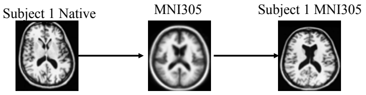
B_0 Distortion Correction



- Can only fix metric distortion
- Dropout is lost forever

Spatial Normalization

- Transform volume into another volume (or surface)
- New volume is an "atlas" space
- Align brains of different subjects so that a given voxel represents the "same" location.
- Preparation for comparing across subjects
- Not always done in preprocessing (FSL)
- More in Group Analysis later in this talk



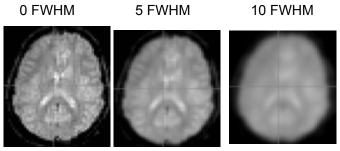
Spatial Smoothing

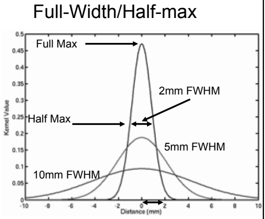
- Replace voxel value with a weighted average of nearby voxels (spatial convolution)
- 3D (volume), 2D (surface)
- Improves SNR
- Improves intersubject registration
- Can have a dramatic effect on your results

Spatial Smoothing

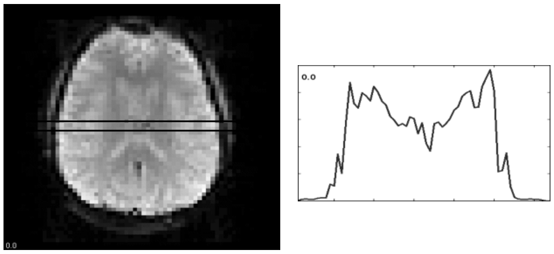
- Spatially convolve image with Gaussian kernel.
- Kernel sums to 1
- Full-Width/Half-max: FWHM = σ/sqrt(log(256))

σ = standard deviation of the Gaussian

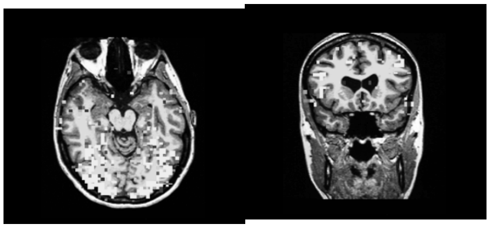




Spatial Smoothing



Effect of Smoothing on Activation



- Working memory paradigm
- FWHM: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 mm

Preprocessing

- Start with a 4D data set

1. Motion Correction - Interpolation
2. Slice-Timing Correction
3. B_0 Distortion Correction - Interpolation
4. Spatial Normalization - Interpolation
5. Spatial Smoothing – Interpolation-like

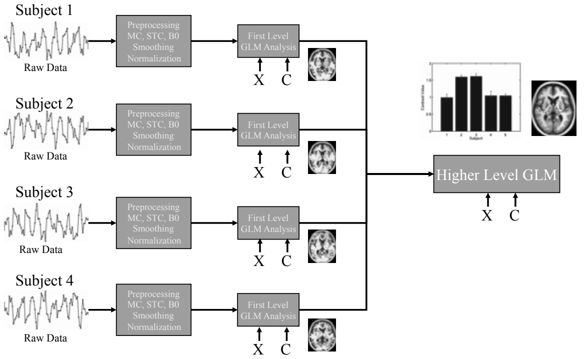
- End with a 4D data set

- Can be done in other orders
- Not all are done

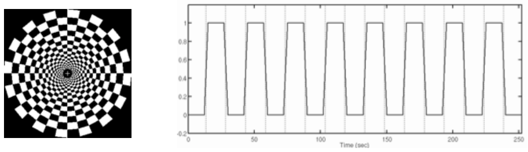
---

fMRI Time-Series Analysis

fMRI Analysis Overview

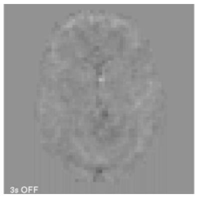


Visual/Auditory/Motor Activation Paradigm

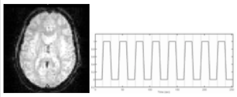


15 sec ‘ON’, 15 sec ‘OFF’

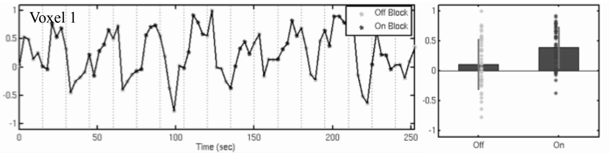
- **Flickering Checkerboard**
- **Auditory Tone**
- **Finger Tapping**



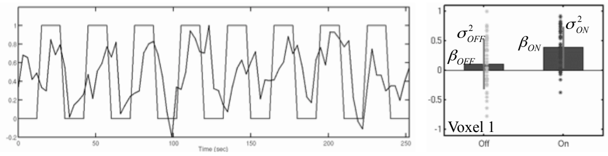
Block Design: 15s Off, 15s On



Stimulus Schedule
Paradigm File



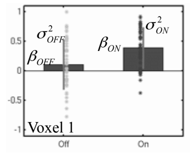
Temporal Correlation Between Paradigm and Raw Time Course



Amplitude of correlation (β) related to amount of neural activation (hopefully)

Hypotheses and Contrasts

<u>Hypothesis</u>: the neural activity during the ON Block is greater than, less than, or simply different than that during the OFF Bock.

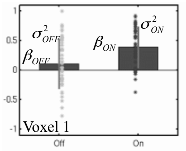


<u>Null Hypothesis (H_0)</u>: neural activity is the same during ON and OFF Blocks.

Statistical Test: β_{ON} != β_{OFF}

$\beta_{ON} - \beta_{OFF} = 0$ → “Contrast”

Contrasts and Inference



$$t = \frac{\beta_{ON} - \beta_{OFF}}{\sqrt{\frac{(N_{ON}-1)\sigma^2_{ON} + (N_{OFF}-1)\sigma^2_{OFF}}{(N_{ON}+N_{OFF}-2)^2}}}$$

$\beta_{ON}, \sigma^2_{ON}, N_{ON}$ – Mean, Var, N in ON

$\beta_{OFF}, \sigma^2_{OFF}, N_{OFF}$ – Mean, Var, N in OFF

$$\boxed{\text{Contrast} = \beta_{ON} - \beta_{OFF}} \quad \boxed{\text{Var(Contrast)} = \frac{(N_{ON}-1)\sigma^2_{ON} + (N_{OFF}-1)\sigma^2_{OFF}}{(N_{ON}+N_{OFF}-2)^2}}$$

H_0: Contrast = 0

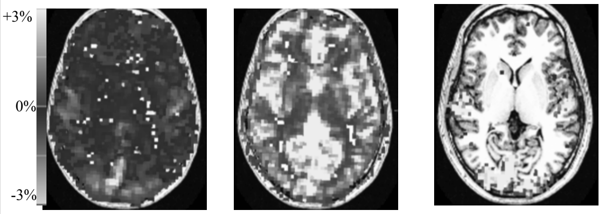
P-value is probability that H_0 is true (computed from t)

If probability is very low, then “Reject” H0 → declare a positive

Voxel 1: $p = 10^{-11}$, sig = $-\log10(p) = 11$ (repeat for every voxel)

Note: z, t, F monotonic with p

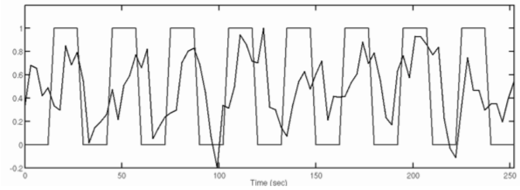
Statistical Parametric Map (SPM)



Contrast Amplitude $\beta_{ON} - \beta_{OFF}$ CON, COPE, CES	Variance of Contrast (Error Bars) VARCOPE, CESVAR	H_0 Significance *t*-Map (*p*,*z*,*F*) (Thresholded *p*<0.01) sig = −log10(*p*)

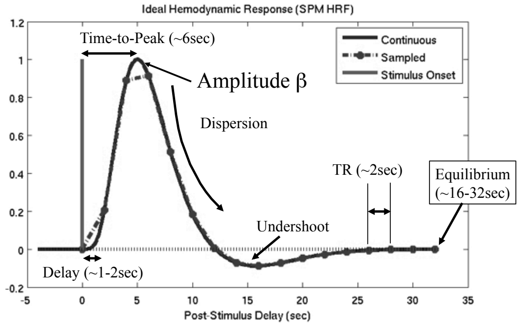
"Massive Univariate Analysis"
-- Analyze each voxel separately

Hemodynamics



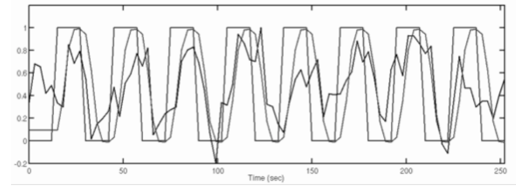
- Delay
- Dispersion
- Grouping by simple time point inaccurate

Hemodynamic Response Function (HRF)

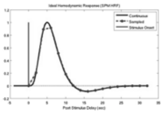


Amplitude β related to the amount of neural firing

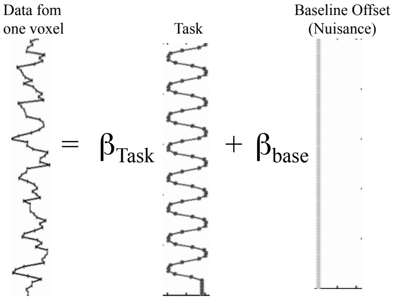
Convolution Stimulus with HRF



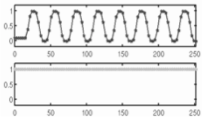
- Shifts, rolls off; more accurate
- Loose ability to simply group time points
- More complicated analysis
- General Linear Model (GLM)



GLM



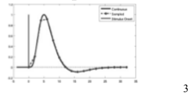
$$= \beta_{Task} \quad + \beta_{base}$$



$\beta_{base}=\beta_{off}$

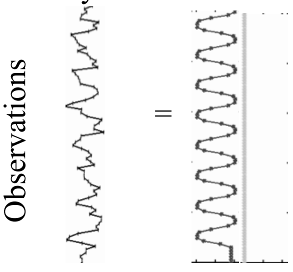
$\beta_{Task}=\beta_{on}-\beta_{off}$

- •Implicit Contrast
- •HRF Amplitude



Matrix Model

$$y \quad = \quad X \quad * \quad \beta$$



$$\begin{bmatrix} \beta_{Task} \\ \beta_{base} \end{bmatrix}$$

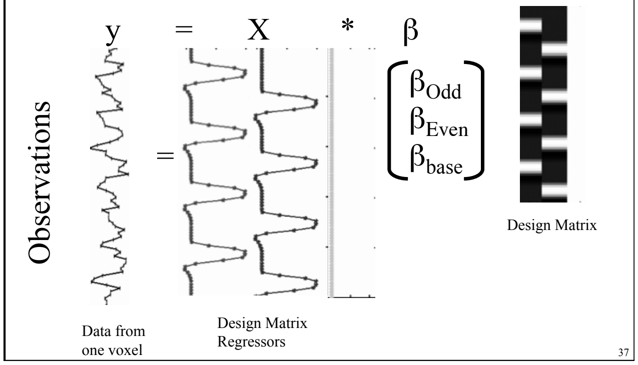
Vector of Regression Coefficients ("Betas")

Design Matrix

Data from one voxel

Design Matrix Regressors

Two Task Conditions



y = X * β

Observations

=

$\begin{bmatrix} \beta_{\text{Odd}} \\ \beta_{\text{Even}} \\ \beta_{\text{base}} \end{bmatrix}$

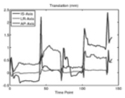
Design Matrix

Data from
one voxel

Design Matrix
Regressors

First Level Design

- Every stimulus type gets a column in the design matrix
- Every stimulus type gets a regression coefficient (β)
- β related to neural firing
- Contrasts created by adding/subtracting βs
- "Nuisance" factors can be added as more columns
  - Low frequency drifts (DCT, polynomial)
  - Motion correction regressors
  - Physiological (eg, pulse and respiration)
  - CSF or WM waveforms
- Functional Connectivity waveforms added as a column



All factors get a column and a regression coefficient

For those interested in the math …

$y = X\beta + n, \quad y = s + n, \quad n \sim N(0, \sigma_n^2)$

$\hat{\beta} = (X^T X)^{-1} X^T y$ Parameter Estimates

$\hat{\sigma}_n^2 = \frac{\hat{n}^T \hat{n}}{DOF}$ Residual Variance, $\hat{n} = y - X\hat{\beta}$

$\hat{\gamma} = C\hat{\beta}$ Contrast

$\hat{\sigma}_\gamma^2 = \hat{\Sigma}_\gamma = \frac{1}{J}\left(C(X^T X)^{-1} C^T\right)\hat{\sigma}_n^2$ Contrast Variance Estimate

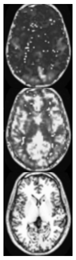
$J = \text{rows in } C$

$\mathrm{t}_{\mathrm{DOF}} = \frac{\hat{\gamma}}{\hat{\sigma}_\gamma} = \frac{C\hat{\beta}}{\sqrt{\left(C(X^T X)^{-1} C^T\right)\hat{\sigma}_n^2}}$ t - Test (univariate)

$\mathrm{F}_{\mathrm{DOF,J}} = \hat{\gamma}^T \hat{\Sigma}_\gamma^{-1} \hat{\gamma}$ F - Test (multivariate)

Time Series Analysis Summary

- Correlational
- Design Matrix (HRF shape)
- Estimate HRF amplitude (Parameters)
- Contrasts to test hypotheses
- Results at each voxel:
  - Contrast Value
  - Contrast Value Variance
  - *p*-value
- Pass Contrast Value and Variance up to higher level analyses



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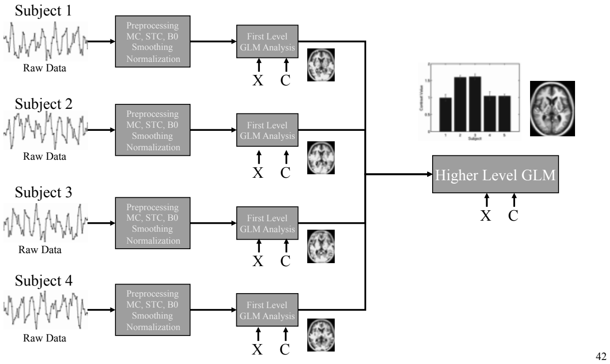
fMRI Group Analysis

---

fMRI Analysis Overview



Subject 1
Raw Data
Preprocessing MC, STC, B0 Smoothing Normalization
First Level GLM Analysis
X C

Subject 2
Raw Data
Preprocessing MC, STC, B0 Smoothing Normalization
First Level GLM Analysis
X C

Subject 3
Raw Data
Preprocessing MC, STC, B0 Smoothing Normalization
First Level GLM Analysis
X C

Subject 4
Raw Data
Preprocessing MC, STC, B0 Smoothing Normalization
First Level GLM Analysis
X C

Higher Level GLM
X C

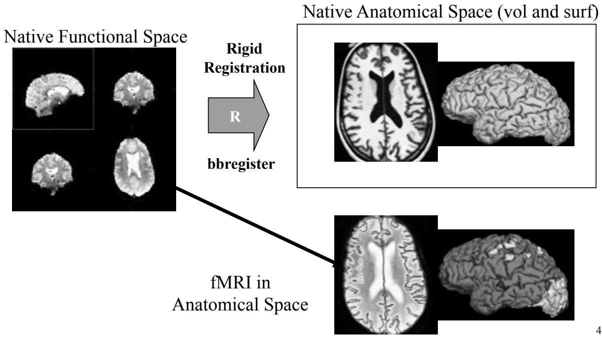
Overview

- Spatial Normalization
- Goal of Group Analysis
- Types of Group Analysis
  - Random Effects, Mixed Effects, Fixed Effects
- Multi-Level General Linear Model (GLM)

Spatial Normalization

- Transform fMRI data to an Atlas Space where it can be compared voxel-by-voxel across subjects
- Multi-step procedure:
  1. Register fMRI to anatomical
  2. Register anatomical to atlas space
  3. Transform fMRI to atlas space
  4. Merge data
- Volume and/or Surface atlas spaces

Step 1 (vol and surf): Register fMRI with Anatomical



Native Anatomical Space (vol and surf)

Native Functional Space

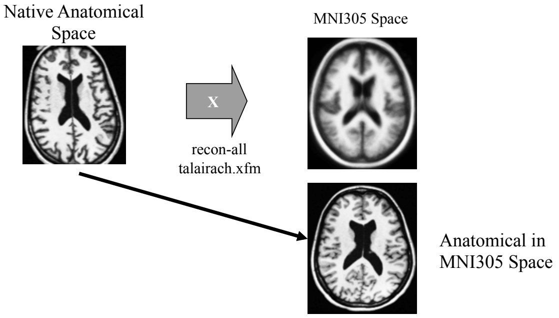
Rigid Registration

R

bbregister

fMRI in Anatomical Space

Step 2 (vol): Register Anatomical with MNI305 (Talairach)



Native Anatomical Space

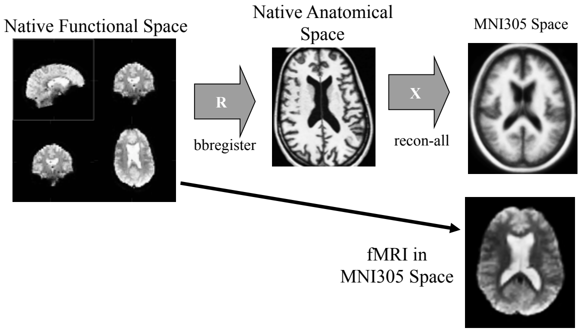
MNI305 Space

X

recon-all
talairach.xfm

Anatomical in MNI305 Space

Step 3 (vol): Combine Steps 1 and 2



Native Functional Space

Native Anatomical Space

MNI305 Space

R

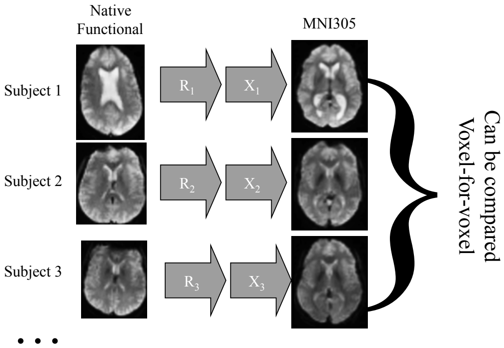
bbregister

X

recon-all

fMRI in MNI305 Space

Step 4 (vol): Merge Subjects



Native Functional

MNI305

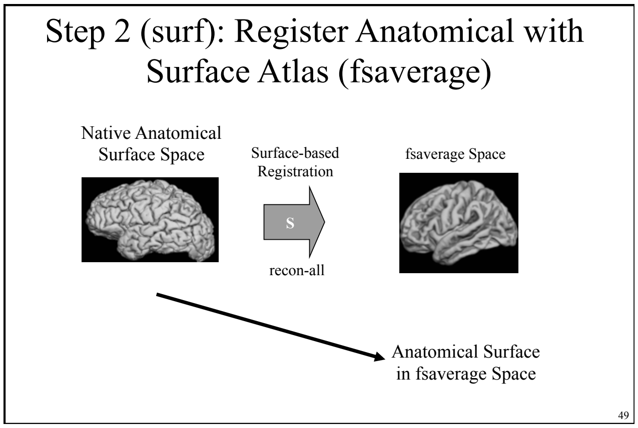
Subject 1 R_1 X_1

Subject 2 R_2 X_2

Subject 3 R_3 X_3

• • •

Can be compared
Voxel-for-voxel



Step 2 (surf): Register Anatomical with Surface Atlas (fsaverage)

Native Anatomical Surface Space

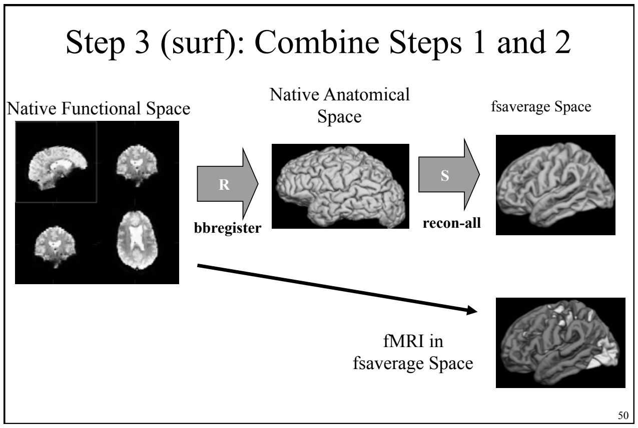
Surface-based Registration

S

recon-all

fsaverage Space

Anatomical Surface in fsaverage Space



Step 3 (surf): Combine Steps 1 and 2

Native Functional Space

R

bbregister

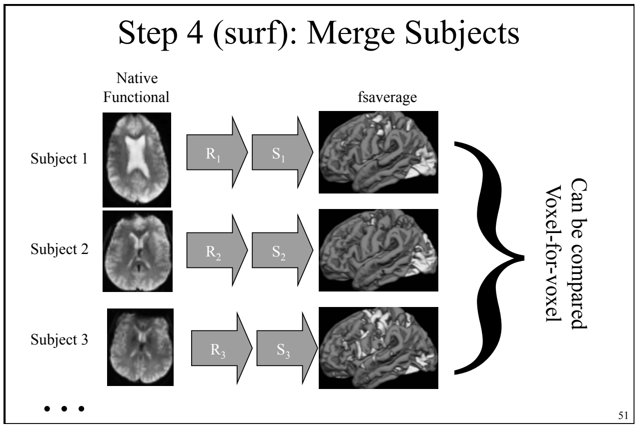
Native Anatomical Space

S

recon-all

fsaverage Space

fMRI in fsaverage Space



Step 4 (surf): Merge Subjects

Native Functional

fsaverage

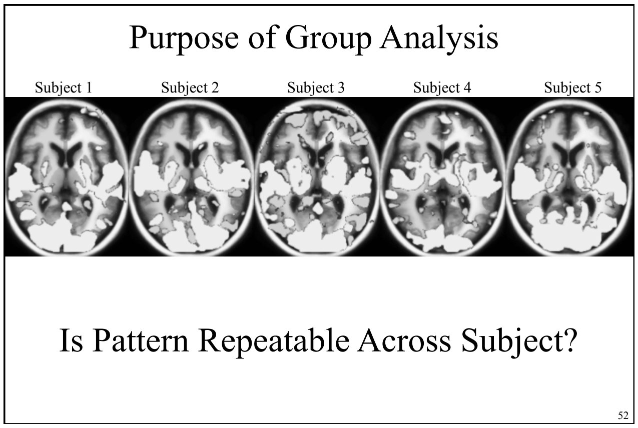
Subject 1 R_1 S_1

Subject 2 R_2 S_2

Subject 3 R_3 S_3

• • •

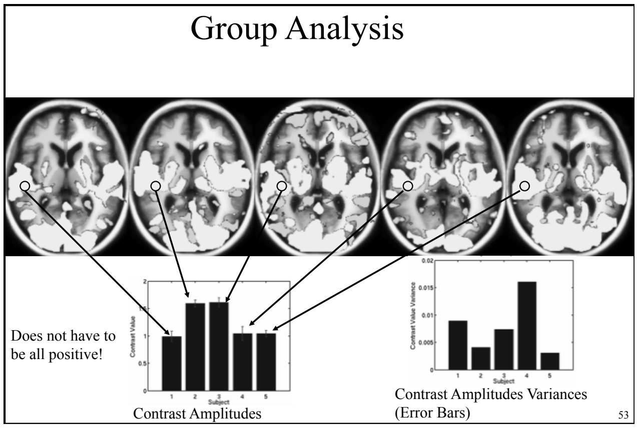
Can be compared Voxel-for-voxel



Purpose of Group Analysis

Subject 1 Subject 2 Subject 3 Subject 4 Subject 5

Is Pattern Repeatable Across Subject?

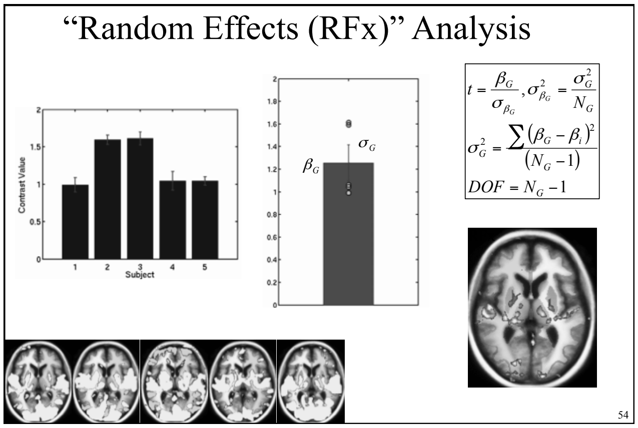


Group Analysis

Does not have to be all positive!

Contrast Amplitudes

Contrast Amplitudes Variances (Error Bars)



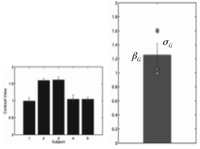
"Random Effects (RFx)" Analysis

$$t = \frac{\beta_G}{\sigma_{\beta_G}}, \sigma_{\beta_G}^2 = \frac{\sigma_G^2}{N_G}$$

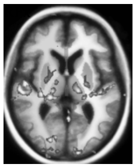
$$\sigma_G^2 = \frac{\sum (\beta_G - \beta_i)^2}{(N_G - 1)}$$

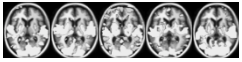
$$DOF = N_G - 1$$

"Random Effects (RFx)" Analysis

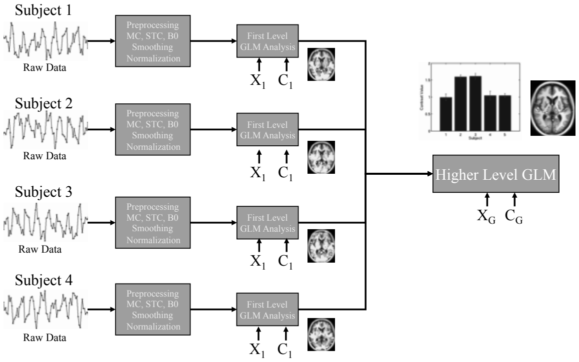


- Model Subjects as a Random Effect
- Variance comes from a single source: variance across subjects
  - Mean at the <u>population</u> mean
  - Variance of the <u>population</u> variance
- Does not take first-level noise into account (assumes 0)
- "Ordinary" Least Squares (OLS)
- Usually less activation than individuals





fMRI Analysis Overview



Subject 1
Raw Data
Preprocessing MC, STC, B0 Smoothing Normalization
First Level GLM Analysis
X_1 C_1

Subject 2
Raw Data
Preprocessing MC, STC, B0 Smoothing Normalization
First Level GLM Analysis
X_1 C_1

Subject 3
Raw Data
Preprocessing MC, STC, B0 Smoothing Normalization
First Level GLM Analysis
X_1 C_1

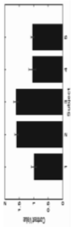
Subject 4
Raw Data
Preprocessing MC, STC, B0 Smoothing Normalization
First Level GLM Analysis
X_1 C_1

Higher Level GLM
X_G C_G

Higher Level GLM Analysis

$$y = X * \beta$$

Observations (Low-Level Contrasts)

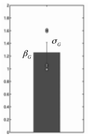


$$= \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} \begin{bmatrix} \beta_G \end{bmatrix}$$

Data from one voxel

Design Matrix (Regressors)

Vector of Regression Coefficients ("Betas")



Contrast Matrix:
$C = [1]$
$\text{Contrast} = C*\beta = \beta_G$

One-Sample Group Mean (OSGM)

Summary

- Preprocessing – MC, STC, B_0, Normalize, Smooth
- First Level GLM Analysis – Design matrix, HRF, Nuisance
- Contrasts, Hypothesis Testing – contrast matrix
- Group Analysis
  - Random Effects (Mixed and Fixed also possible)
  - Multi-level GLM (Design and Contrast Matrices)

fMRI Analysis with the FreeSurfer Functional Analysis Stream (FS-FAST)

Preprocessing, First Level Analysis, and Group Analysis

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Overview

- Atlas Spaces
- Directory Structure
- Preprocessing
- Setting up First-Level Analysis and Contrasts
- Group Analysis
  - Setting up
  - Correction for multiple comparisons

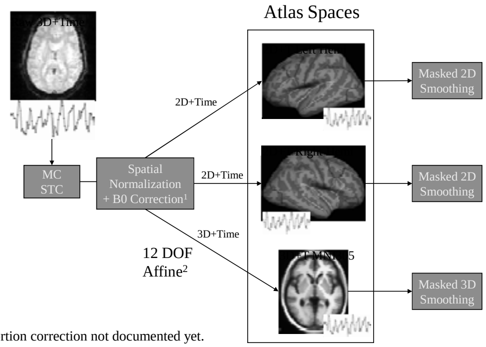
FSFAST

- Time-series functional analysis
  - Event-related, Blocked, Retinotopy, Functional Connectivity
- Built on FreeSurfer
- Surface-, Volume-, ROI-based
- Group Analysis
- Highly Automated
- Command-line driven
- Matlab/Octave, AFNI, and FSL used in the background

Philosophy

- Respect the inherent geometry of the brain structures (Smoothing and Clustering)
- Cortex – 2D
- Subcortical – 3D
- Requires that analysis be done in three spaces:
  - Left Hemisphere
  - Right Hemisphere
  - Subcortical Areas
- Not simple volumetric-based for all voxels!

FS-FAST Preprocessing



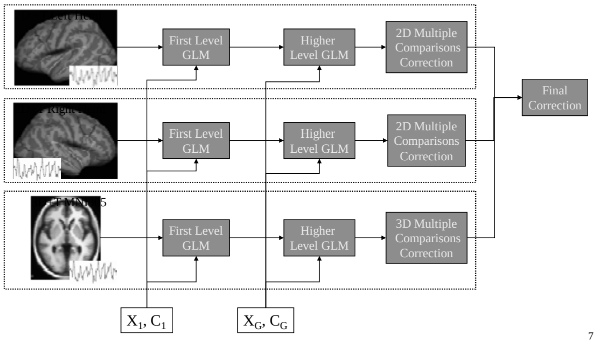
Atlas Spaces

[1] B0 distortion correction not documented yet.

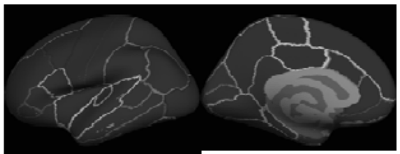
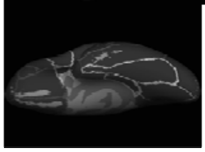
[2] Eventually will be done with CVS.

FS-FAST Analysis

Atlas Space
Masked, Smoothed

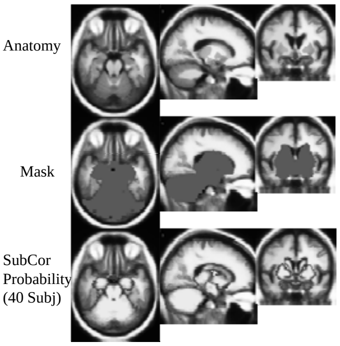


Surface Masking

- Remove medial wall
- Intersect with functional brain mask
- 2D Smoothing only inside mask
- Later individual subjects masks merged (intersection).

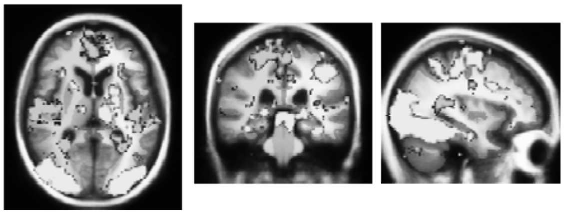
Volume (Subcortical) Masking



- Remove most of cortex
- Remove some WM and CSF
- Intersect with functional brain mask
- 3D Smoothing only inside mask
- Later individual subjects masks merged (intersection).

Tip: use compressed NIFTI files (nii.gz)

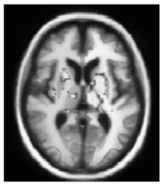
Typical Volume-based Analysis



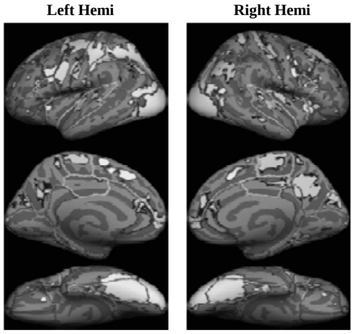
Single map, activation in both cortical and subcortical GM.

fBIRN Group n=18, distractor-vs-fix

FSFAST Analysis



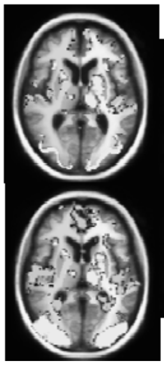
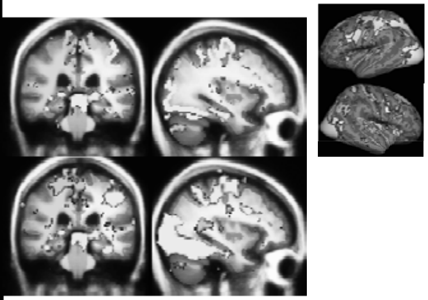
Subcortical (no cortical)



Three mutually exclusive maps

Recombining Cortical and Subcortical

Visualization only!!

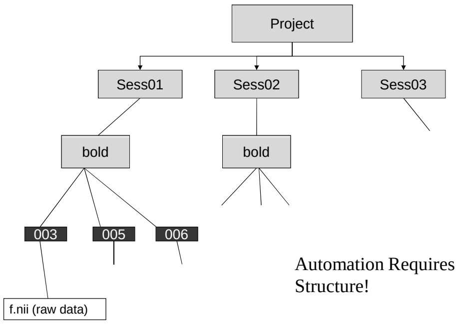
Correction for Multiple Comparisons

- Cluster-based
- Performed separately in each space
  - 2D clustering for Left and Right Hemispheres
  - 3D clustering for MNI305
  - Cluster table for each individual space
- Final cluster table is union of individual spaces

FSFAST Pipeline Summary

1. Analyze anatomicals in FreeSurfer
2. Unpack each subject (dcmunpack,unpacksdcmdir)
3. Create subjectname file.
4. Copy paradigm files into run directories
5. Configure analyses (mkanalysis-sess, mkcontrast-sess)
6. Preprocess (preproc-sess)
7. First Level Analysis (selxavg3-sess)
8. Higher Level Analysis (isxconcat-sess, mri_glmfit)
9. Correction for Multiple Comparisons (mri_glmfit-sim)

FSFAST Directory Structure



Automation Requires Structure!

1. Project

2. Session

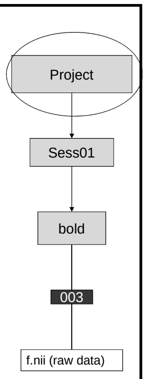
3. Functional Subdirectory (FSD, “bold”)

4. Run

5. Raw Time-Series Data

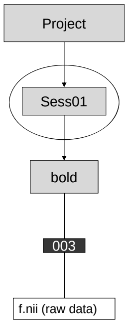
Project Directory

- Folder where all/most of your data reside (can use symbolic links to data too)
- Directory where you will run most commands
- NOT the same as $SUBJECTS_DIR



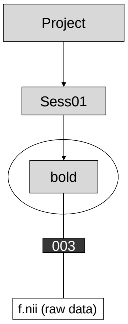
Session Directory

- All the data collected between the time you put a subject into the scanner until you take him/her out.
  - May include data across “breaks”
- All one subject
- Data from one subject may be spread over different sessions (eg, longitudinal study)
- Session does not necessarily equal Subject
- Folder name can be anything.



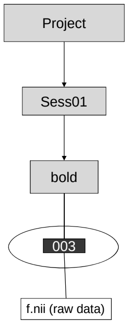
Functional Subdirectory (FSD, “bold”)

- All the data associated with a given paradigm
- Most people just have one paradigm and so only one FSD
- Usually called “bold”
- Default is “bold”

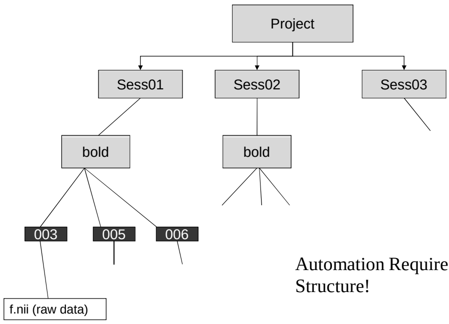


Run Folder/Directory

- All the data collected between pressing the “Apply” button and the end of the scan.
- Eg, 150 time points (TPs)
- Raw functional data stored in this folder
- Usually called “f.nii” or “f.nii.gz”
- Raw data will be in “native functional space”, eg, 64x64x30, 3.125mm x 3.125mm x 6mm
- Folder name will be 3-digit, zero-padded number, eg, “002”, “014”



FSFAST Directory Structure



1. Project

2. Session

3. Functional Subdirectory (FSD, “bold”)

4. Run

5. Raw Time-Series Data

Automation Requires Structure!

Setting Up the Directory Structure

Things you need to do before running automated commands:

1. Unpack raw data from DICOM
2. Add paradigm files
3. Add subjectname file

---

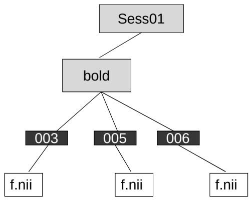
1. Unpacking: Creating the Directory Structure from DICOM Files

- unpacksdcmdir – Siemens only
- dcmunpack – Siemens or GE (not sure about Philips)
- Manually

```
Getting help:
   dcmunpack -help

Get a summary of the scans in a DICOM directory
   dcmunpack –src dicomdir -martinos

 Unpack:
   cd ProjectDir
   dcmunpack –src dicomdir -martinos
      –trg sess01
      –run 3 bold nii f.nii
      –run 5 bold nii f.nii
      –run 6 bold nii f.nii
```



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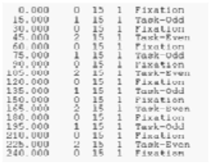
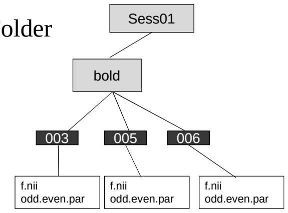
2. Add “Paradigm” File(s)

- Codes Stimulus Schedule
- Simple Text File
- Manually copy into Run Folder

odd.even.par

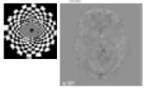


```
  0.000    0   15   1   Fixation
 15.000    1   15   1   Task-Odd
 30.000    0   15   1   Fixation
 45.000    2   15   1   Task-Even
 60.000    0   15   1   Fixation
 75.000    1   15   1   Task-Odd
 90.000    0   15   1   Fixation
105.000    2   15   1   Task-Even
120.000    0   15   1   Fixation
135.000    1   15   1   Task-Odd
150.000    0   15   1   Fixation
165.000    2   15   1   Task-Even
180.000    0   15   1   Fixation
195.000    1   15   1   Task-Odd
210.000    0   15   1   Fixation
225.000    2   15   1   Task-Even
240.000    0   15   1   Fixation
```

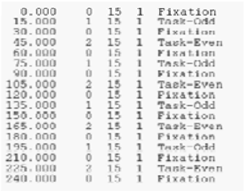


- All have the same name
- May have different content
- Different codings have different names

Paradigm File



- Codes Stimulus Schedule (and Weight)
- Four Columns
  1. Onset Time (Since Acq of 1st Saved Volume)
  2. Stimulus Code (0, 1, 2 ,3 …)
  3. Stimulus Duration
  4. Stimulus Weight (default is 1)
  5. Any other columns ignored
- Simple Text File
- Code 0 Always Fixation/NULL
- Weight for parametric modulation

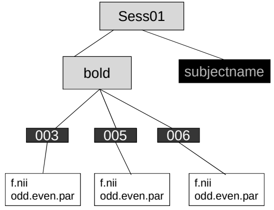


```
  0.000    0   15   1   Fixation
 15.000    1   15   1   Task-Odd
 30.000    0   15   1   Fixation
 45.000    2   15   1   Task-Even
 60.000    0   15   1   Fixation
 75.000    1   15   1   Task-Odd
 90.000    0   15   1   Fixation
105.000    2   15   1   Task-Even
120.000    0   15   1   Fixation
135.000    1   15   1   Task-Odd
150.000    0   15   1   Fixation
165.000    2   15   1   Task-Even
180.000    0   15   1   Fixation
195.000    1   15   1   Task-Odd
210.000    0   15   1   Fixation
225.000    2   15   1   Task-Even
240.000    0   15   1   Fixation
```

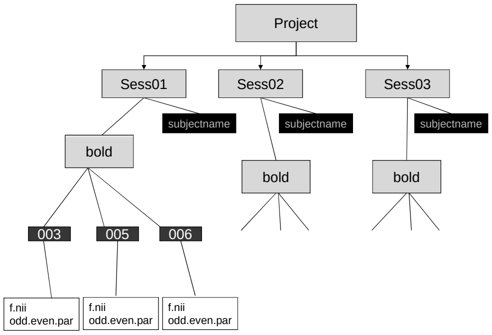
---

3. Add “subjectname” file

- Integration with FreeSurfer anatomical analysis
- Subject name is name passed to recon-all, eg,
  - recon-all –all –subject bert
  - $SUBJECTS_DIR/bert
- Create a text file called “sess01/subjectname”, the content of the file will be, eg, “bert” (no quotes)



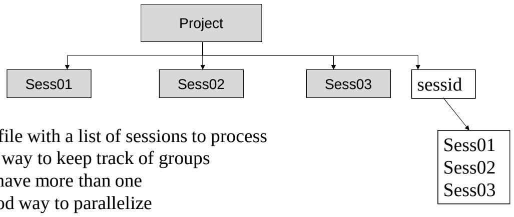
FSFAST Directory Structure


Project
Sess01
Sess02
Sess03
subjectname
subjectname
subjectname
bold
bold
bold
003
005
006
f.nii
odd.even.par
f.nii
odd.even.par
f.nii
odd.even.par

1. Project
2. Session
3. Functional Subdirectory (FSD, “bold”)
4. Run
5. Raw Time-Series Data

Congratulations: You are now ready to start running the “automated” commands … but before you do …

Session Id File (“SessId”)


Project
Sess01
Sess02
Sess03
sessid
Sess01
Sess02
Sess03

- Text file with a list of sessions to process
- Easy way to keep track of groups
- Can have more than one
- A good way to parallelize

FS-FAST Commands will often take a SessId file as input:

selxavg3-sess –sf sessid …

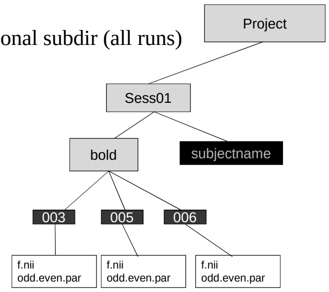
Will run for all sessions found in sessid

Alternatively, selxavg3-sess –s Sess01 –s Sess02 –s Sess03

OK, now you are ready to start running the “automated” commands …

First-Level Analysis

- Time-series analysis
- Everything inside of a functional subdir (all runs)
- Preprocessing
- GLM Analysis


Project
Sess01
bold
subjectname
003
005
006
f.nii
odd.even.par
f.nii
odd.even.par
f.nii
odd.even.par

Preprocessing

1. Registration Template Creation
2. Motion Correction
3. Slice-timing correction (if using)
4. Functional-Anatomical Registration
5. Mask creation
6. Intensity normalization, Part 1
7. Resampling raw time series to mni305, lh, and rh
8. Spatial smoothing

- B0 distortion correction not documented yet

Preprocessing Command

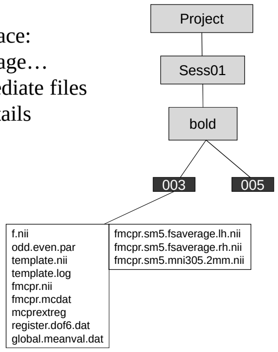
preproc-sess	Command Name
–sf sessids	Session Id File
–surface fsaverage lhrh	Surface-based (lh and rh of fsaverage)
–mni305	Volume-based in mni305 (subcort)
–fwhm 5	Smoothing 5mm FWHM
–per-run	Run-wise MC+registration

preproc-sess -help

- Preprocess all runs of all sessions
- Can take a long time!

Directory Structure after Preprocessing

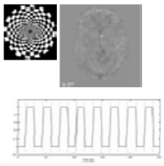
- Final data in atlas space:
  - fmcpr.sm5.fsaverage…
- Lots of other intermediate files
- Lots more boring details

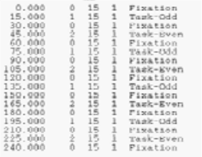


First Level GLM Analysis

- Specify Task Model
  - Event-related or Blocked
  - AB-Blocked (Periodic two condition)
  - Retinotopy
  - Task timing (Paradigm file)
  - Hemodynamic Response Function (HRF)
  - Contrasts
- Specify Nuisance and Noise Models
  - Low frequency drifts
  - Time point exclusion
  - Motion Regressors
  - Other (Physiology, RETROICOR)
  - Temporal Whitening

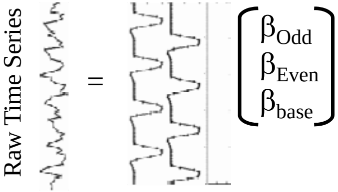
Example: Odd Even Blocks





```
  0.000    0  15  1  Fixation
 15.000    1  15  1  Task-Odd
 30.000    0  15  1  Fixation
 45.000    2  15  1  Task-Even
 60.000    0  15  1  Fixation
 75.000    1  15  1  Task-Odd
 90.000    0  15  1  Fixation
105.000    2  15  1  Task-Even
120.000    0  15  1  Fixation
135.000    1  15  1  Task-Odd
150.000    0  15  1  Fixation
165.000    2  15  1  Task-Even
180.000    0  15  1  Fixation
195.000    1  15  1  Task-Odd
210.000    0  15  1  Fixation
225.000    2  15  1  Task-Even
240.000    0  15  1  Fixation
```

$$y = X * \beta$$



Data from one voxel

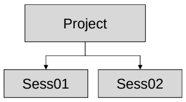
Design Matrix Regressors

First Level GLM Analysis: Workflow

- Do these two steps once regardless of number of sessions:
  1. Configure "Analysis" – collection of parameters, mkanalysis-sess
  2. Create Contrasts (mkcontrast-sess)
  - Don't even need data to do this
- Do this for each session:
  - Perform Analysis (selxavg3-sess)

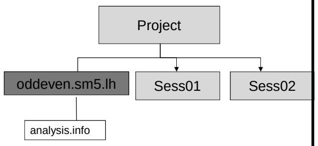
Configure First Level GLM Analysis

```
cd ProjectDir
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```



Configuration: Analysis Name

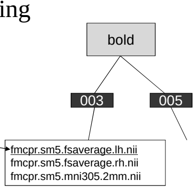
```
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```



Analysis Name – name used to reference this collection of parameters. Use a different name for a different set of parameters.

Configuration: Preprocessing

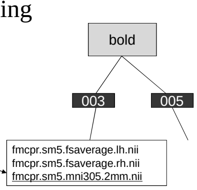
```
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```



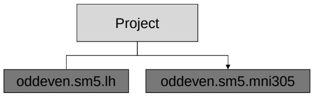
Preprocessing options indicate what the source time-series file name will be.

Configuration: Preprocessing

```
mkanalysis-sess
  -analysis oddeven.sm5.mni305
  -mni305
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```

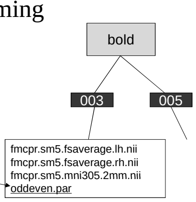


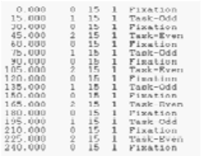
A different analysis is needed for each space (lh, rh, and mni305)



Configuration: Stimulus Timing

```
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```





```
  0.000    0  15  1  Fixation
 15.000    1  15  1  Task-Odd
 30.000    0  15  1  Fixation
 45.000    2  15  1  Task-Even
 60.000    0  15  1  Fixation
 75.000    1  15  1  Task-Odd
 90.000    0  15  1  Fixation
105.000    2  15  1  Task-Even
120.000    0  15  1  Fixation
135.000    1  15  1  Task-Odd
150.000    0  15  1  Fixation
165.000    2  15  1  Task-Even
180.000    0  15  1  Fixation
195.000    1  15  1  Task-Odd
210.000    0  15  1  Fixation
225.000    2  15  1  Task-Even
240.000    0  15  1  Fixation
```

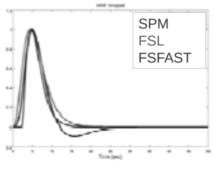
Configuration: Task Type

```
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```

Event-related and blocked are the same. Other possibilities are:
  -abblocked
  -retinotopy

Configuration: HRF Model

```
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```



- SPM Canonical HRF
- 0 Derivatives

Other options:
 -fslhrf NDerivaties
 -fir PreStim TotTimeWindow
-gammafit 2.25 1.25

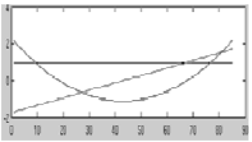
Configuration: Reference Event Duration

```
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```

Just set this to the duration of your event in seconds.

Configuration: Nuisance Drift Modeling

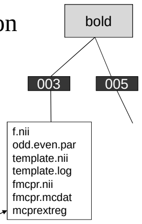
```
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```



2nd Order Polynomial. <u>This is the default</u>.
  0: mean offset
  1: temporal trend
  2: quadratic trend

Can also specify a high-pass filter with
  -hpf CutOffHz
where CutOffHz is the cut-off frequency in Hz (eg, .01). Careful with this.

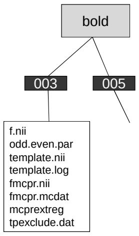
Configuration: Nuisance Motion



```
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```

Use Motion Correction parameters as nuisance regressors (good idea?). Can specify arbitrary regressor files with "–nuisreg file N".

Configuration: Excluding Time Points



```
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```

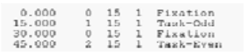
Skip the 1st 4 time points. Do not need to adjust stimulus timing. Alternative: "-tpexclude tpexclude.dat" to remove any TP. Good for motion.

Configuration: Why TR and NCond?

```
mkanalysis-sess
  -analysis oddeven.sm5.lh
  -surface fsaverage lh
  -fwhm 5
  -paradigm oddeven.par
  -event-related
  -spmhrf 0
  -refeventdur 4
  -polyfit 2
  -mcextreg
  -nskip 4
  -TR 2 -nconditions 2
  -per-run
```

It could get this from the data and paradigm files, but this command is set up to run without the need of any data, so it needs to know the TR and number of conditions.

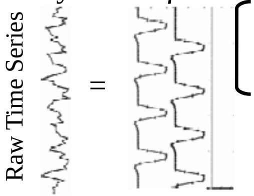
Number of conditions is the number of Non-Fixation/Non-NULL conditions.
2 = Odd + Even



```
 0.000    0   15   1   Fixation
15.000    1   15   1   Task-Odd
30.000    0   15   1   Fixation
45.000    2   15   1   Task-Even
```

Contrasts: Odd Even Blocks

$$y = X * \beta$$



$$\begin{bmatrix} \beta_{Odd} \\ \beta_{Even} \\ \beta_{base} \end{bmatrix}$$

- Two task conditions
- One nuisance regressor
- Need weight for each condition

Does the hemodynamic response amplitude to the Odd stimulus differ from that of Even?

$\gamma = 1*\beta_{Odd} -1* \beta_{Even}$

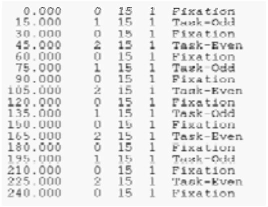
C = [+1 -1] Contrast Matrix

Configuration: Contrasts

- Linear combination of regression coefficients (COPE, CON)
- Weight for each condition
- Embodies a hypothesis: Does the hemodynamic response amplitude to the Odd stimulus differ from that of Even? C = [+1 -1]

```
mkcontrast-sess
 -analysis oddeven.sm5.lh
 -contrast odd-vs-even
 -a 1
 -c 2
```

paradigm file

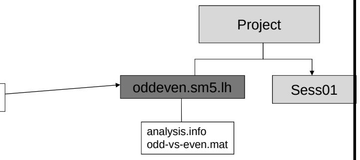


```
  0.000    0   15   1   Fixation
 15.000    1   15   1   Task-Odd
 30.000    0   15   1   Fixation
 45.000    2   15   1   Task-Even
 60.000    0   15   1   Fixation
 75.000    1   15   1   Task-Odd
 90.000    0   15   1   Fixation
105.000    2   15   1   Task-Even
120.000    0   15   1   Fixation
135.000    1   15   1   Task-Odd
150.000    0   15   1   Fixation
165.000    2   15   1   Task-Even
180.000    0   15   1   Fixation
195.000    1   15   1   Task-Odd
210.000    0   15   1   Fixation
225.000    2   15   1   Task-Even
240.000    0   15   1   Fixation
```

Configuration: Contrasts

- -analysis as created by mkanalysis-sess

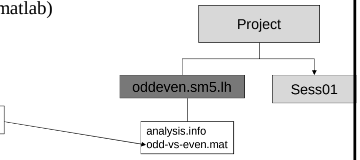
```
mkcontrast-sess
 -analysis oddeven.sm5.lh
 -contrast odd-vs-even
 -a 1
 -c 0
```



Configuration: Contrasts

- -contrast ContrastName
- name used to reference this contrast
- unique within the given analysis
- Creates ContrastName.mat (matlab)

```
mkcontrast-sess
 -analysis oddeven.sm5.lh
 -contrast odd-vs-even
 -a 1
 -c 0
```

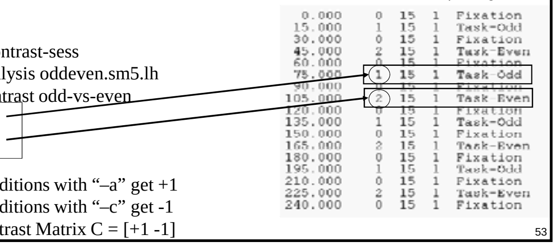


Specifying Contrast Weights

- “Active” – positive, “Control” – negative
- Odd vs Even means Odd-Even
- Paradigm File Encoding

paradigm file

```
mkcontrast-sess
 -analysis oddeven.sm5.lh
 -contrast odd-vs-even
 -a 1
 -c 2
```



```
  0.000    0   15   1   Fixation
 15.000    1   15   1   Task-Odd
 30.000    0   15   1   Fixation
 45.000    2   15   1   Task-Even
 60.000    0   15   1   Fixation
 75.000    1   15   1   Task-Odd
 90.000    0   15   1   Fixation
105.000    2   15   1   Task-Even
120.000    0   15   1   Fixation
135.000    1   15   1   Task-Odd
150.000    0   15   1   Fixation
165.000    2   15   1   Task-Even
180.000    0   15   1   Fixation
195.000    1   15   1   Task-Odd
210.000    0   15   1   Fixation
225.000    2   15   1   Task-Even
240.000    0   15   1   Fixation
```

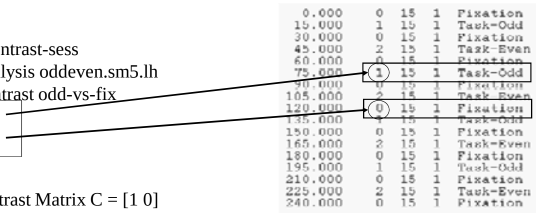
Conditions with “–a” get +1
Conditions with “–c” get -1
Contrast Matrix C = [+1 -1]

Odd vs Fixation

- “Active” – positive, “Control” – implicit
- Odd vs Fixation means Odd-Fixation
- Do not need Fixation-Odd
- Paradigm file coding

paradigm file

```
mkcontrast-sess
 -analysis oddeven.sm5.lh
 -contrast odd-vs-fix
 -a 1
 -c 0
```



```
  0.000    0   15   1   Fixation
 15.000    1   15   1   Task-Odd
 30.000    0   15   1   Fixation
 45.000    2   15   1   Task-Even
 60.000    0   15   1   Fixation
 75.000    1   15   1   Task-Odd
 90.000    0   15   1   Fixation
105.000    2   15   1   Task-Even
120.000    0   15   1   Fixation
135.000    1   15   1   Task-Odd
150.000    0   15   1   Fixation
165.000    2   15   1   Task-Even
180.000    0   15   1   Fixation
195.000    1   15   1   Task-Odd
210.000    0   15   1   Fixation
225.000    2   15   1   Task-Even
240.000    0   15   1   Fixation
```

Contrast Matrix C = [1 0]
Implicit contrast vs Fixation

Configuration: Three Conditions

1. Happy
2. Sad
3. Mad

Hypothesis: response to Happy is different than that to Mad

```
mkcontrast-sess
 -analysis faces.sm5.lh
 -contrast happy-vs-mad
 -a 1
 -c 3
```

Note: Condition 2 (Sad) not represented (set to 0)
C = [1 0 -1]

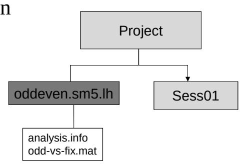
Hypothesis: response to Happy is different than the <u>average</u> response to Sad and Mad (Happy =? (Sad+Mad)/2)

```
mkcontrast-sess
 -analysis faces.sm5.lh
 -contrast happy-vs-sadmad
 -a 1
 -c 2
 -c 3
```

C=[1 -0.5 -0.5]

Configuration: Summary

- mkanalysis-sess, mkcontrast-sess
- Need configuration for lh, rh, and mni305
- Specify: Preproc, Task, Nuisance, Noise, Contrasts
- Does not do analysis, just creates configuration
- Do <u>once</u> for each parameter set (space)
- Do <u>once</u> regardless of number of sessions
- Should take a few seconds to run

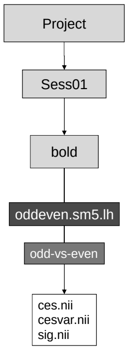


First-Level GLM Analysis

```
cd ProjectDir
selxavg3-sess –sf sessidfile –analysis oddeven.sm5.lh
```

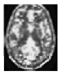
- Finds raw data, paradigm file, external regressors, etc
- Constructs design and contrast matrices
- Combines runs together using “smart” concatenation (1st and 2nd level)
- Performs GLM fit at each voxel
- Tests contrasts at each voxel
- All sessions specified in sessid file
- May take a few hours, depending on how many sessions
- Does not re-run if data are “up-to-date”
- Will run preprocessing if not done already
- Requires matlab or octave

After First Level Analysis…



1. Project
2. Session
3. Functional Subdirectory (FSD, “bold”)
4. Analysis Folder
5. Contrast Folder
6. Contrast Values

ces - contrast effect size, COPE (FSL), CON (SPM)



cesvar - contrast variance VARCOPE (FSL)

sig = -log10(p)

First Level Analysis: Visualization

Surface-based analyses:

```
tksurfer-sess –s session –analysis oddeven.sm5.lh –c odd-vs-fix
tksurfer-sess –s session –a oddeven.sm5.rh –c odd-vs-fix
```

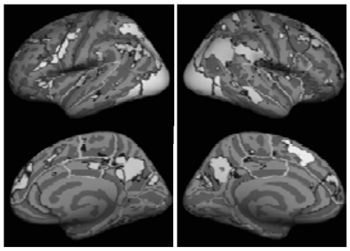
Volume-based analyses (freeview can also be used):

```
tkmedit-sess –s session –a oddeven.sm5.mni305 –c odd-vs-fix
```

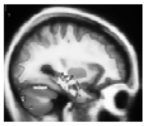
One session at a time (-s session, NOT –sf sessidfile)
Can specify multiple contrasts, eg,
–c odd-vs-fix –c even-vs-fix –c odd-vs-even
Or all contrasts with “-call”

Note Shortcut: “-a” instead of “-analysis” and “-c instead of –contrast”

First Level Analysis: Visualization

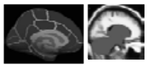


No activation in medial wall



No activation in cortex

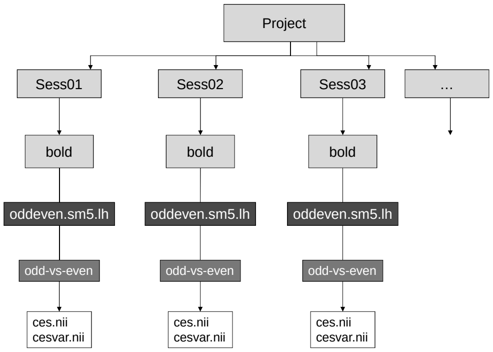
Masking



Individual subject shown on fsaverage anatomy
Can show/analyze on individual anatomy.

fBIRN probe-vs-fix

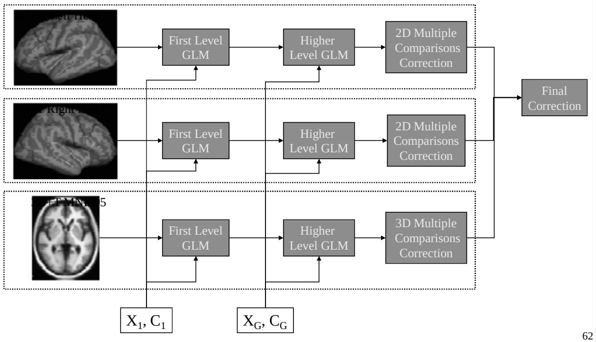
After First Level Analysis…



1. Project
2. Session
3. Functional Subdirectory (FSD, “bold”)
4. Analysis Folder
5. Contrast Folder
6. Contrast Values

FS-FAST Analysis

Atlas Space
Masked, Smoothed



First Level GLM → Higher Level GLM → 2D Multiple Comparisons Correction

First Level GLM → Higher Level GLM → 2D Multiple Comparisons Correction

First Level GLM → Higher Level GLM → 3D Multiple Comparisons Correction

Final Correction

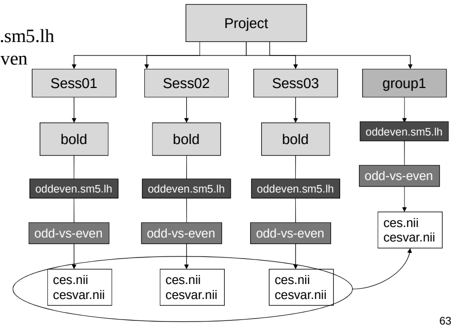
X_1, C_1

X_G, C_G

Group/Higher Level Analysis: Consolidation

cd ProjectDir
isxconcat-sess
-analysis oddeven.sm5.lh
-contrast odd-vs-even
-sf group1.sessid
-o group1

isxconcat-sess -help



Project

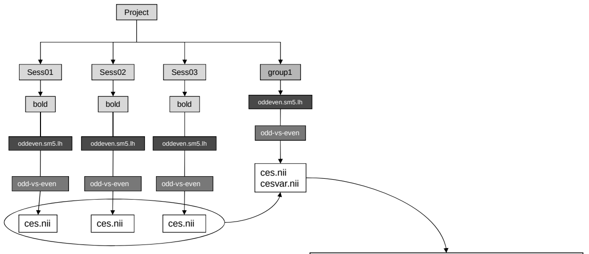
Sess01 / Sess02 / Sess03 / group1

bold → oddeven.sm5.lh → odd-vs-even → ces.nii cesvar.nii

group1 → oddeven.sm5.lh → odd-vs-even → ces.nii cesvar.nii

Like mris_preproc
in anatomical stream

Group/Higher Level Analysis: Consolidation



Project

Sess01 / Sess02 / Sess03 / group1

bold → oddeven.sm5.lh → odd-vs-even → ces.nii

group1 → oddeven.sm5.lh → odd-vs-even → ces.nii cesvar.nii

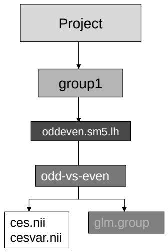
isxconcat-sess
-analysis oddeven.sm5.lh
-contrast odd-vs-even
-sf group1.sessid
-o group1

One frame/time point for each session
Order is IMPORTANT!!!
Order will be as listed in group1.sessid

Group/Higher Level Analysis

```
cd ProjectDir
cd group1/oddeven.sm5.lh/odd-vs-even

mri_glmfit
  --surf fsaverage lh
  --y ces.nii
  --wls cesvar.nii
  --fsgd group1.fsgd
  --C group.con1.mtx
  --C group.con2.mtx
  --glmdir glm.group
```



Project → group1 → oddeven.sm5.lh → odd-vs-even → ces.nii cesvar.nii / glm.group

See FreeSurfer Group Analysis, including correction for multiple comparisons.
http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/GroupAnalysis
mri_glmfit –help

Group/Higher Level Analysis

```
mri_glmfit
  --surf fsaverage lh
  --y ces.nii
  --wls cesvar.nii
  --fsgd group1.fsgd
  --C group.con1.mtx
  --C group.con2.mtx
  --glmdir glm.group
```

- Surface-based analysis on the left hemisphere of fsaverage.
- For right hemisphere, use
  “–surf fsaverage rh”.
- For mni305, so not specify –surf.

Group/Higher Level Analysis

```
mri_glmfit
  --surf fsaverage lh
  --y ces.nii
  --wls cesvar.nii
  --fsgd group1.fsgd
  --C group.con1.mtx
  --C group.con2.mtx
  --glmdir glm.group
```

Lower-level contrast input data, one frame/time point for each subject.

Group/Higher Level Analysis

```
mri_glmfit
  --surf fsaverage lh
  --y ces.nii
  --wls cesvar.nii
  --fsgd group1.fsgd
  --C group.con1.mtx
  --C group.con2.mtx
  --glmdir glm.group
```

Lower-level contrast variances, one frame/time point for each subject. Performs weighted least squares (Pseudo-Mixed Effects)

Group/Higher Level Analysis

```
mri_glmfit
  --surf fsaverage lh
  --y ces.nii
  --wls cesvar.nii
  --fsgd group1.fsgd
  --C group.con1.mtx
  --C group.con2.mtx
  --glmdir glm.group
```

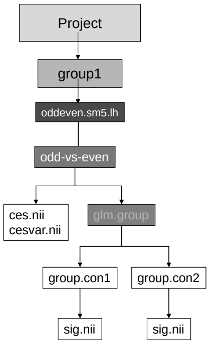
FSGD file must have same order of sessions as sessidfile used when running isxconcat-sess

```
isxconcat-sess
     -analysis oddeven.sm5.lh
     -contrast odd-vs-even
     -sf group1.sessid
     -o group1
```

Group/Higher Level Analysis

```
mri_glmfit
  --surf fsaverage lh
  --y ces.nii
  --wls cesvar.nii
  --fsgd group1.fsgd
  --C group.con1.mtx
  --C group.con2.mtx
  --glmdir glm.group
```

- Higher Level/Group contrasts.
- Eg, Normal vs Schizophrenia
- Easily confused with lower level contrasts (eg, odd-vs-even).



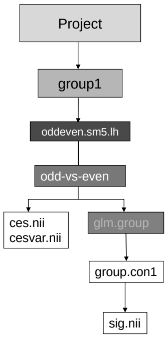
Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at p < .05

```
cd ProjectDir
cd group1/oddeven.sm5.lh/odd-vs-even

mri_glmfit-sim
  --glmdir glm.group
  --cache pos 2
  --cwpvalthresh .05
  --3spaces
```

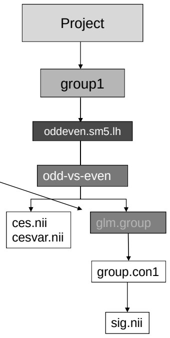
Masking



Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir glm.group
  --cache pos 2
  --cwpvalthresh .05
  --3spaces
```



Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir glm.group
  --cache pos 2
  --cwpvalthresh .05
  --3spaces
```

- Use pre-cached simulation results
- positive group contrast
- voxelwise threshold = 2 (p<.01)
- Can use another simulation or permutation

Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir glm.group
  --cache pos 2
  --cwpvalthresh .05
  --3space
```

Cluster-wise threshold p<.05

Surface-based Correction for Multiple Comparisons

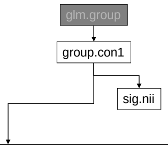
- 2D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir glm.group
  --cache pos 2
  --cwpvalthresh .05
  --3spaces
```

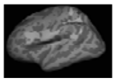
Bonferroni correction across 3 spaces: lh, rh, and subcort

Correction for Multiple Comparisons Output (Surface)

```
mri_glmfit-sim
  --glmdir glm.group
  --cwpvalthresh .05
  --cache pos 2
  --3spaces
```

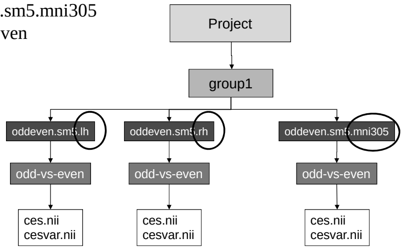


<u>cache.th20.pos.sig.cluster.nii</u> – map of significance of clusters
<u>cache.th20.pos.sig.ocn.annot</u> – annotation of significant clusters
<u>cache.th20.pos.sig.cluster.summary</u> – text file of cluster table (clusters, sizes, MNI305 XYZ, and their <u>significances</u>)



Group MNI305 Analysis

```
isxconcat-sess
    -analysis oddeven.sm5.mni305
    -contrast odd-vs-even
    -sf group1.sessid
    -o group1
```



Group Subcortical (MNI305) Analysis

```
mri_glmfit
  --y ces.nii
  --wls cesvar.nii
  --fsgd group1.fsgd
  --C group.con1.mtx
  --C group.con2.mtx
  --glmdir glm.group
```

- Command-line is very similar to surface
- No "–surf fsaverage lh"

Surface-base command

```
mri_glmfit
  --surf fsaverage lh
  --y ces.nii
  --wls cesvar.nii
  --fsgd group1.fsgd
  --C group.con1.mtx
  --C group.con2.mtx
  --glmdir glm.group
```

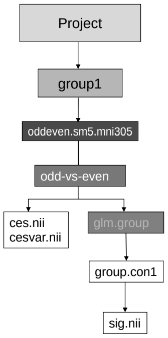
Volume-based Correction for Multiple Comparisons

- 3D Cluster-based Correction at p < .05

```
cd ProjectDir
cd group1/oddeven.sm5.mni305/odd-vs-even

mri_glmfit-sim
  --glmdir glm.group
  --grf pos 2
  --cwpvalthresh .05
  --3spaces
```

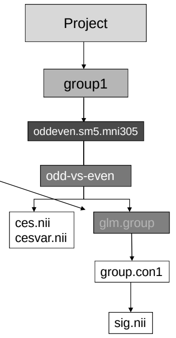
Masking



Volume-based Correction for Multiple Comparisons

- 3D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir glm.group
  --grf pos 2
  --cwpvalthresh .05
  --3spaces
```



Volume-based Correction for Multiple Comparisons

- 3D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir glm.group
  --grf pos 2
  --cwpvalthresh .05
  --3spaces
```

- Use Gaussian Random Field
- positive group contrast
- voxelwise threshold = 2 (p<.01)
- Can use simulation or permutation

Volume-based Correction for Multiple Comparisons

- 3D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir glm.group
  --grf pos 2
  --cwpvalthresh .05
  --3spaces
```

Cluster-wise threshold p<.05

Volume-based Correction for Multiple Comparisons

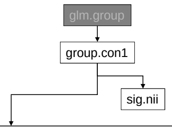
- 3D Cluster-based Correction at p < .05

```
mri_glmfit-sim
  --glmdir glm.group
  --grf pos 2
  --cwpvalthresh .05
  --3spaces
```

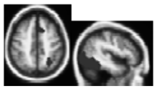
Bonferroni correction across 3 spaces: lh, rh, and subcort

Correction for Multiple Comparisons Output (Volume)

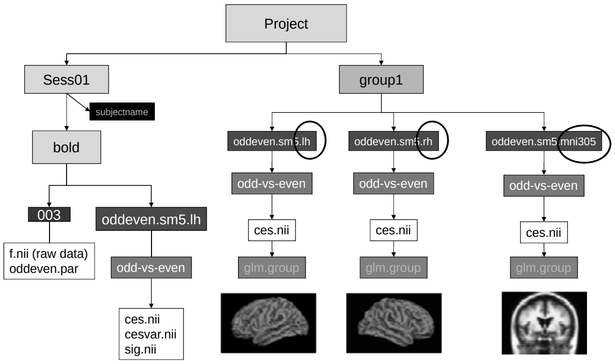
```
mri_glmfit-sim
  --glmdir glm.group
  --grf pos 2
  --cwpvalthresh .05
  --3spaces
```



grf.th2.pos.sig.cluster.nii – map of significance of clusters
grf.th2.pos.sig.ocn.nii – segmentation of significant clusters
grf.th2.pos.sig.cluster.summary – text file of cluster table (clusters, sizes, MNI305 XYZ, and their significances)



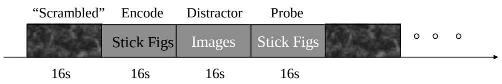
Full Group Analysis



FSFAST Pipeline Summary

1. Analyze anatomicals in FreeSurfer
2. Unpack each subject (dcmunpack,unpacksdcmdir)
3. Create subjectname file.
4. Copy paradigm files into run directories
5. Configure analyses (mkanalysis-sess, mkcontrast-sess)
6. Preprocess (preproc-sess)
7. First Level Analysis (selxavg3-sess)
8. Higher Level Analysis (isxconcat-sess, mri_glmfit)
9. Correction for Multiple Comparisons (mri_glmfit-sim)
10. Publish (publish-sess ☺)

Tutorial: Working Memory Task



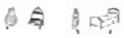
0. “Scrambled” – low-level baseline, no response

1. Encode – series of passively viewed stick figures

Distractor – respond if there is a face

2. Emotional
3. Neutral

Probe – series of two stick figures (forced choice)

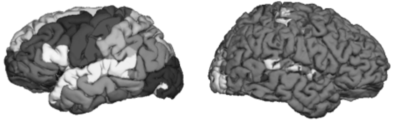


4. Following Emotional Distractor
5. Following Neutral Distractor

fBIRN: Functional Biomedical Research Network (www.nbirn.net)

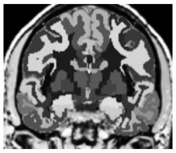
- freesurfer.net

Multimodal Integration: DTI/fMRI Integration, Surface Analysis



Quick Review: DTI Integration

- View FA, etc., on subject’s anatomical volume
- Intensity ROI Study: Average FA, etc., inside of White Matter Parcellation ROIs (wmparc.mgz)



wmparc.mgz

Quick Review: DTI Integration

- Motion/Eddy Current Correction (MC Template)
- Usually a low-b volume
- Use for registration template

```
bbregister --mov mctemplate.nii --s subject --init-fsl --lta register.lta
```

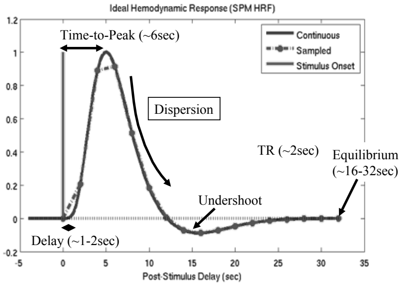
```
freeview -v mctemplate.nii:reg=register.lta -f $SUBJECTS_DIR/subject/surf/?h.white
```

- First-Level (Individual) Analysis
- Fit Tensor Model
- Maps: FA (0-1), ADC, Eigenvectors, etc
- All in alignment with MC Template!!!!

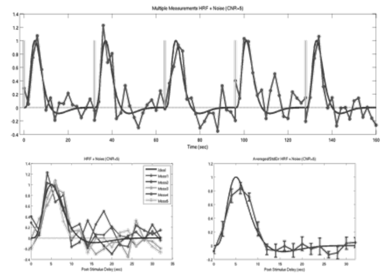
fMRI Integration

- Visualize individual fMRI results on
    - surface
    - volume
- ROI Volume Study:
    - Count number of voxels above threshold in an anatomical ROI
- ROI Intensity Study:
    - Average HRF inside of an ROI
- Surface-based fMRI group analysis

Hemodynamic Response (BOLD)

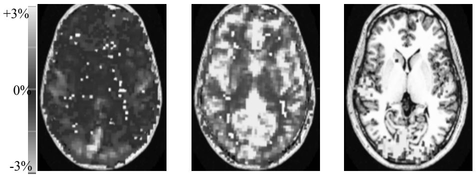


Multiple Presentations/Averaging

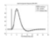


Individual Output: HRF Amp, HRF Var, p/z/t/F

Statistical Parametric Map (SPM)



Contrast **Amplitude**
CON, COPE, CES



"Massive Univariate Analysis"
-- Analyze each voxel separately

Contrast Amplitude
Variance
(Error Bars)
VARCOPE, CESVAR

Significance
t-Map (p,z,F)
(Thresholded p<.01)
sig=-log10(p)

---

fMRI Preprocessing Overview

- Motion Correction (MC Template)
- Use reference/template for registration

- bbregister --mov template.nii --bold --s subject --init-fsl --lta register.lta
- freeview -v template.nii:reg=register.lta -f $SUBJECTS_DIR/subject/surf/?h.white

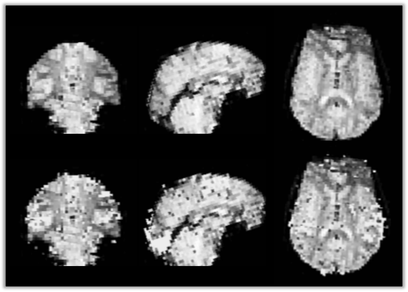
- Do not use <u>nonlinear</u> resampling to Talairach/MNI space. Best work in native space!
- Do not spatially smooth (3D) (set fwhm=0 in SPM...) we do not smooth in volume, rather on surface later!

---

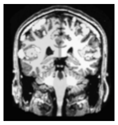
fMRI Analysis Overview

- First-Level (Individual) Analysis
  - HRF Amplitude (or Contrast of Amplitudes)
    - cope (FSL),
    - CON (SPM),
    - ces (FSFAST)
  - Variance of Amplitude
    - varcope (FSL), ??? (SPM), cesvar (FSFAST)
  - Activation/Significance Maps:
    - z, t, F
    - sig (-log10(p))
- All in alignment with MC Template!!!!

Reference and Map



Volume Viewing



```
freeview -tkmedit subject orig.mgz
   -aparc+aseg
   -overlay sig.nii -reg register.lta
   -fthresh 2 -fmax 4
```

sig.nii – significance map in native functional space.
Could have been z, t, or F map as well.

register.lta – FreeSurfer registration file

fthresh – lower threshold (value depends on map).
You can change this in the interface.

fmax – saturation threshold. (value depends on map).
You can change this in the interface.

aparc+aseg – display aparc+aseg.mgz.
You can load this from the interface, too.

Volume Viewing

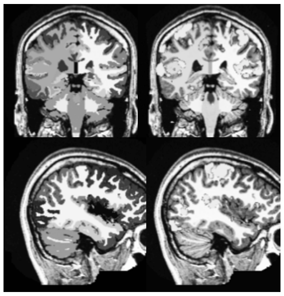
```
freeview -v $SUBJECTS_DIR/fbirn-anat-101.v4/mri/orig.mgz \
            $SUBJECTS_DIR/fbirn-anat-101.v4/mri/aparc+aseg.mgz:colormap=lut:opacity=.3 \
            sig.nii:colormap=heat:heatscale=2,3.0,4:reg=register.lta
```

sig.nii – significance map in native functional space.
Could have been z, t, or F map as well.

register.lta – FreeSurfer registration file

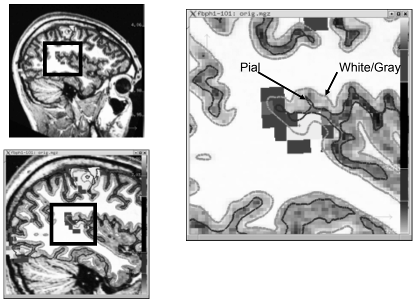
aparc+aseg – display aparc+aseg.mgz.
You can load this from the interface, too.

Volume Viewing

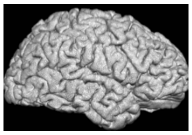


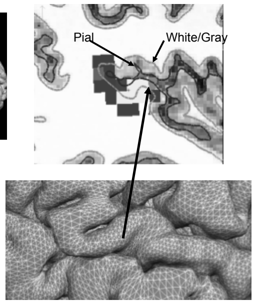
- Red/Yellow +
- Blue/Cyan -
- Seg Opacity
- ROI Average
- ROI Count

Sampling onto the Surface



Sampling onto the Surface

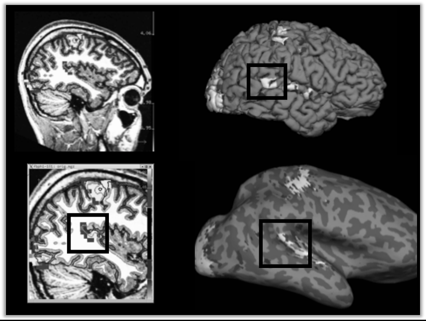




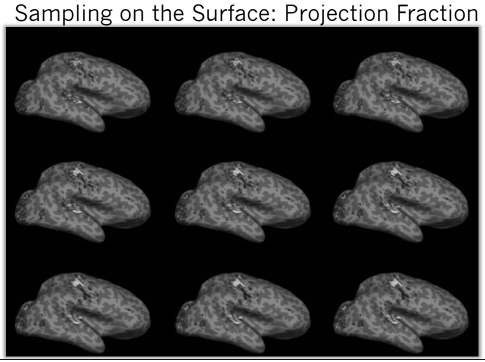
- White/Gray
- Pial
- Half Way
- Average

Projection Fraction
--projfrac 0.5

Sampling onto the Surface



Sampling on the Surface: Projection Fraction



Surface Viewing

Resample HRF Contrast Significance to left hemisphere

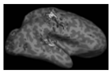
```
mri_vol2surf \
  --mov sig.nii \                → map in native functional space
  --reg register.lta \           → FreeSurfer registration file
  --hemi lh \                    → hemisphere
  --projfrac 0.5 \               → projection fraction (half)
  --o lh.sig.mgh                 → output (Nvertices-x-1 mgh format)
```

Note similarity to bbregister command!

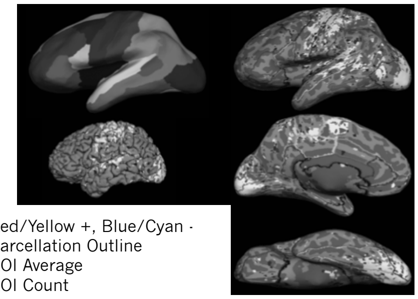
Load HRF Contrast Significance as overlay

```
freeview -f $SUBJECTS_DIRsubject/surf/lh.inflated:annot=aparc.annot:overlay=lh.sig.mgh:overlay_threshold=2,5 \
          -viewport 3d

tksurfer subject lh inflated -aparc   –overlay lh.sig.mgh
```



Surface Viewing



- Red/Yellow +, Blue/Cyan -
- Parcellation Outline
- ROI Average
- ROI Count

Surface-based Group Analysis

```
mris_preproc
  --hemi lh
  --o lh.fsaverage.ces.mgh
  --iv subject1/ces.nii subject1func/register.lta
  --iv subject2/ces.nii subject2func/register.lta
  --iv subject3/ces.nii subject3func/register.lta
...
```

After that, everything else is the same as a thickness study ...

```
mris_fwhm --i lh.fsaverage.ces.mgh --fwhm 10 \
  --o lh.fsaverage.ces.sm10.mgh --cortex
```

```
mri_glmfit --surf fsaverage lh --cortex \
  --y lh.fsaverage.ces.sm10.mgh ...
```

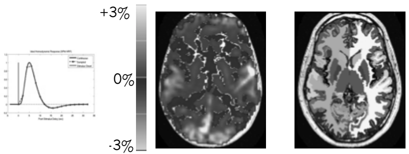
---

fMRI ROI Analysis

- HRF Amplitude
  - Full Anatomical ROI
  - Functionally Constrained ROI
- Volume

---

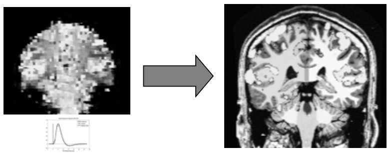
fMRI ROI Analysis



Contrast Amplitude

E.g., average functional HRF amplitudes from voxels inside of superior temporal gyrus (light blue) regardless of significance.

Step 1. Resample HRF Contrast to anatomical space

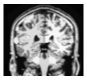


mri_vol2vol \	→ Command name
--mov ces.nii \	→ HRF map in functional space
--reg register.lta \	→ FreeSurfer Registration File
--interp nearest \	→ Nearest neighbor interpolation
--fstarg \	→ Specify anatomical output space
--o ces.anat.mgh	→ Output file in anatomical space

Note similarity to bbregister and mri_vol2surf commands!

Step 2: Average HRF Contrast within ROIs

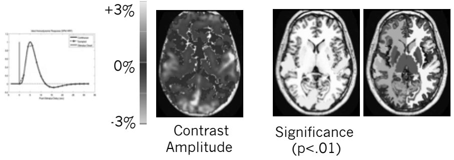
```
mri_segstats
  --seg $SUBJECTS_DIR/subject/mri/aseg.mgz
  --ctab $FREESURFER_HOME/FreeSurferColorLUT.txt
  --i ces.anat.mgh
  --sum ces.aseg.stats
```



Notes:
--seg is the segmentation (e.g., aseg.mgz, aparc+aseg.mgz, etc.)
--ctab is matching color lookup table

Output File: **ces.aseg.stats**
- simple text file with same format aseg.stats
- multiple subjects can be combined with asegstats2table

Average HRF within a Functionally Active area inside of an Anatomical ROI



E.g., average functional HRF amplitudes from voxels inside of superior temporal gyrus (light blue) for voxels that have

1. p<.01 (sig>2) regardless of sign (yellow or blue), or
2. p<.01 (sig>2) for positive activation (yellow only), or
3. p<.01 (sig>2) for negative activation (blue only)

Masked Average HRF within a Functionally Active Area inside of an Anatomical ROI

Resample HRF Contrast Significance to anatomical space

```
mri_vol2vol \
  --mov sig.nii \
  --reg register.lta \
  --interp nearest \
  --fstarg \
  --o sig.anat.mgh
```

Masked average HRF contrast within functionally constrained ROIs (sign independent):

```
mri_segstats \
  --seg $SUBJECTS_DIR/subject/mri/aseg.mgz \
  --ctab $FREESURFER_HOME/FreeSurferColorLUT.txt \
  --i ces.anat.mgh --sum ces.aseg.mask.stats \
  --mask sig.anat.mgh --mask-thresh 2 --mask-sign abs
```

Masked Average HRF within a Functionally Active Area inside of an Anatomical ROI

```
mri_segstats \
  --seg $SUBJECTS_DIR/subject/mri/aseg.mgz \
  --ctab $FREESURFER_HOME/FreeSurferColorLUT.txt \
  --i ces.anat.mgh --sum ces.aseg.mask.stats \
  --mask sig.anat.mgh --mask-thresh 2 --mask-sign abs
```

- Volume in stats file is vol. above threshold (may be 0)
- Sign is important for Average!
  - abs, pos, or neg
  - pos will <u>always</u> result in positive HRF average
  - neg will <u>always</u> result in negative HRF average
  - abs ????
- Careful to avoid circularity

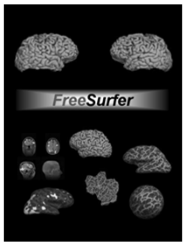
Summary

- Multi/Cross-modal map (HRF Amplitude, FA)
- Multimodal Integration requires a Reference
- A Reference/Template is:
  - Same size as multimodal map
  - In Voxel-to-voxel alignment with map
  - Has better anatomical contrast
    - Baseline functional
    - Low-B DTI
  - Usually a motion corrected template
- Volume and Intensity ROI Analyses
  - Functionally-constrained ROI

Tutorial

1. Registration – manual and automatic registration

2. fMRI Integration (Sensorimotor Paradigm)
   a) Individual
      i. Volume view sig
      ii. Surface view sig
      iii. ROI analysis with & without functional constraint
   b) Group
      i. mris_preproc
      ii. ROI analysis (asegstats2table)



More Registration Techniques

MASSACHUSETTS GENERAL HOSPITAL

---

registration tool summary

- mris_register

- fslregister: bet + flirt
- bbregister

- mri_robust_register

- mri_cvs_register
  - mris_register
  - mri_nl_align

---

registration morph summary

- .dat, .lta, .xfm, .fslmat: encode rigid and affine transformations
  - mri_vol2vol

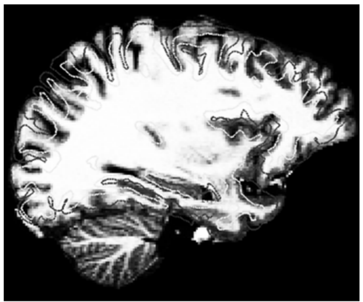
- sphere.reg: encodes spherical morph
  - mris_resample

- .m3z: encode nonlinear volumetric morphs
  - mri_vol2vol

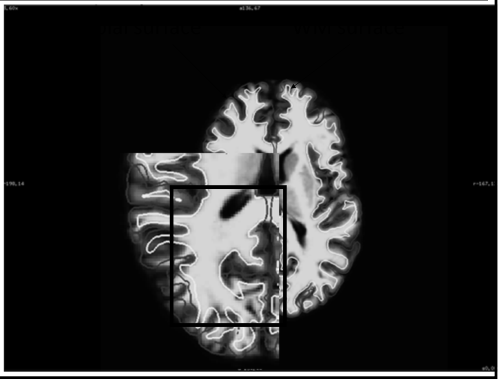
A new registration solution?

- Surface-based (2D) registration does an excellent job of aligning cortical folds, but does not apply to non-cortical structures (e.g. basal ganglia).
- Volumetric (3D) registration applies to the entire brain but does not, in general, align folding patterns.
- Goal: combined their strength

Why aligning folds in the volume is hard…

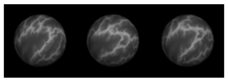


Affine transform of surfaces from one subject mapped to another.

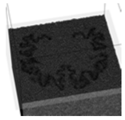


Combined volumetric and surface-based registration (CVS)

- Spherical alignment



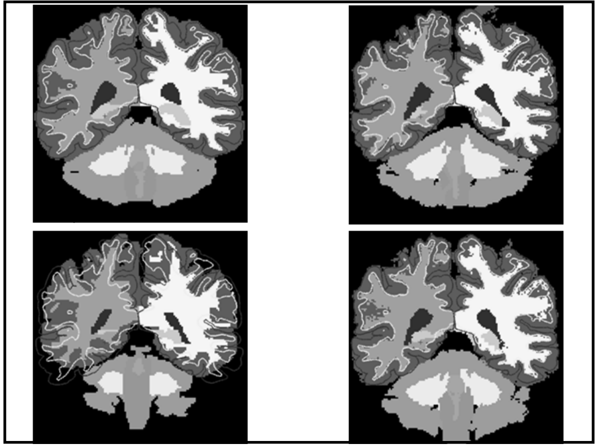
- Elastic propagation of cortical registration results in the 3D volume

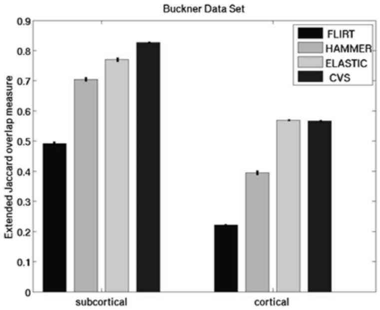


- Volumetric alignment of sub-cortical regions

Resulting morph

Template
Elastic
CVS
Template





Extended Jaccard Coefficient measures: 20 cortical and 21 sub-cortical labels. (The vertical lines represent the standard error of the mean of the measurement.)

G.M. Postelnicu*, L . Zöllei*, B. Fischl: "*Combined Volumetric and Surface Registration*", IEEE Transactions on Medical Imaging (TMI), Vol 28 (4), April 2009, p. 508-522

---

mri_cvs_register --mov subjid

- registering the subject to, by default, the CVS atlas space
- make sure that the SUBJECTS_DIR for *subjid* is correctly set

Optional Arguments

-- template subjid	: subjid for template subject
-- templatedir dir	: recon directory for template (default is SUBJECTS_DIR)
--outdir dir	: output directory for all the results (default is SUBJECTS_DIR/subjid/cvs)

… and many more: use --help

---

mri_cvs_register

Optional Arguments (cont)

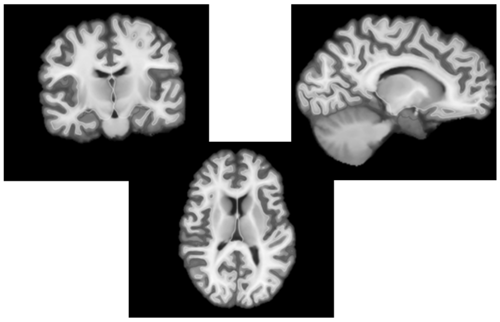
--step1
Only do step 1 (spherical registration).
--step2
Only do step 2 (elastic registration).
--step3
Only do step 3 (volumetric registration).
--noaseg
Do not use aseg volumes in the volumetric registration pipeline (default is 0). Setting this option could shorten significantly the time of registration, however, might also take away from the accuracy of the final results.

mri_cvs_register

Optional Arguments (cont)

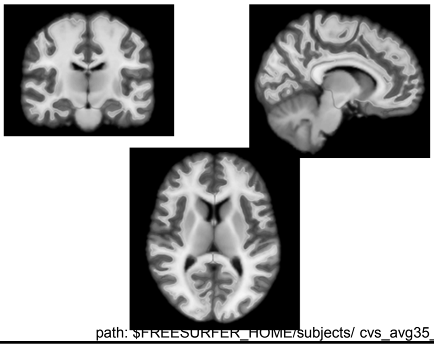
```
--nocleanup
        Do not delete temporary files (default is 0).
--keepelreg
        Do not delete elastic registration (default is 0) outcome.
--cleanall
        Recompute all CVS-related morphs that might have been computed prior to the current
    CVS run (def = 0).
--cleansurfreg
        Recompute CVS-related surface registration morphs that might have been computed
    prior to the current CVS        run (def = 0).
 --cleanelreg
        Overwrite /recompute the CVS-related elastic registration morph that might have been
    computed prior to the current CVS run (default is 0).
--cleanvolreg
        Overwrite / recompute CVS-related volumetric morphs that might have been computed
    prior to the current CVS run (default is 0).
```

CVS atlas



path: $FREESURFER_HOME/subjects/cvs_avg35

CVS atlas in MNI152 space



path: $FREESURFER_HOME/subjects/ cvs_avg35_inMNI152/

related commands

- mri_cvs_check
  - checking whether all files needed for a successful CVS registration are present
- mri_cvs_data_copy
  - copying the CVS-relevant recon directories over to a new location
- mri_vol2vol
  - applying the CVS registration morph to files corresponding to the *moving* subject

Applying CVS morphs

mri_vol2vol

1. applying CVS morph to aseg file

```
mri_vol2vol     --targ templateid --m3z morph.m3z \
                --noDefM3zPath --mov asegvol \
                --o asegvol2CVS --interp nearest \
                --no-save-reg
```

2. applying morph to corresponding diffusion file

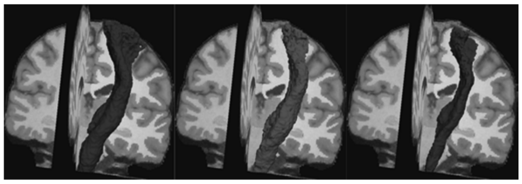
```
mri_vol2vol     --targ templateid --m3z morph.m3z
                --noDefM3zPath --reg 2anat.register.dat
                --mov diffvol --o diffvol2CVS
                --no-save-reg
```

Application of CVS to tractography

- Goal: fiber bundle alignment
- Study: compare CVS to methods directly aligning DWI-derived scalar volumes
- Conclusion: high accuracy cross-subject registration based on structural MRI images can provide improved alignment

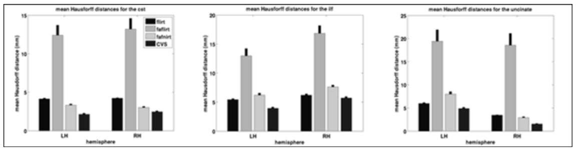
- Zöllei, Stevens, Huber, Kakunoori, Fischl: "*Improved Tractography Alignment Using Combined Volumetric and Surface Registration*", NeuroImage 51 (2010), 206-213

Average tracts after registration mapped to the template displayed with iso-surfaces



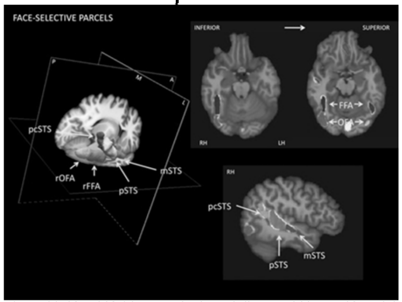
FLIRT FA-FNIRT CVS

Mean Hausdorff distance measures for three fiber bundles



CST ILF UNCINATE

Functional MRI analysis in CVS space



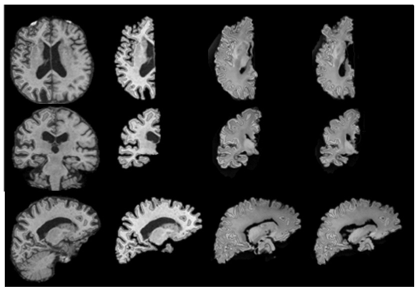
Collaboration with Kami Koldewyn, Joshua Julien and Nancy Kanwisher at MIT

Ongoing development

- Improve CVS capability to register ex-vivo to in-vivo acquisitions
- Implemented MI-based volumetric registration (for CVS step 3) to accommodate intensity profile differences
- Qualitative preliminary results on 4 subjects

- L. Zöllei, Allison Stevens, Bruce Fischl: *Non-linear Registration of Intra-subject Ex-vivo and In-vivo Brain Acquisitions,* Human Brain Mapping, June 2010
- L. Zöllei, B. Fischl, *Automatic segmentation of ex-vivo MRI images using CVS in FreeSurfer, HBM 2011*

Subject 1



Target (in-vivo) Masked target 2-step CVS CVS with MI

FreeSurfer Tutorial and Workshop Quiz

Discuss the answers to these questions with your partner.

What is the difference between a volume and a surface?

- A volume stores information about 3D space, whereas a surface stores 2D space.

Do I have to use two MPRAGEs to run recon-all? Explain.

- No, you do not have to use two structural scans as input to recon-all. If a multi-channel head coil is being used, then generally the SNR will be high enough where averaging two scans is no longer beneficial (and can even worsen a perfectly good scan).

Can FreeSurfer help me select a region of interest and measure certain quantities within? How?

- You can draw a region of interest either in the volume (using tkmedit and the Select Voxels tool) or on the surface (using tkmedit or qdec).

What is fsaverage made of?

- It is constructed of MRI scans of 40 subjects that have been manually segmented. 10 are young adults, 10 are middle-ages, 10 are older cognitively normal, and 10 are older demented patients.

What measures will FreeSurfer give me?

- Volume, Mean Intensity (plus standard deviation, min, and max) of the Subcortical structures, Cortical gray matter, CSF, Cerebellum, White Matter, Ventricles, and Brainstem. Number of vertices, Surface Area, Volume, Thickness, Mean Curvature of the parcellated cortex. Also, Total Gray Matter Volume (cortical + subcortical gray), Supratentorial Volume (everything above the tentorium), Total Cortical Gray Volume (difference between pial and white surface), Subcortical Gray volume (total of all subcortical gm volumes), Total White Matter volume (volume within white surface excluding subcortical gray matter), estimated ICV.

How long does it take for recon-all to finish processing one subject?

- 20-24 hours.

How long would it take you to do this manually?

- To manually label the wm, gm, and subcortical structures of one case will likely take a month.

Why do I have to set so many variables before using FreeSurfer?

- The variables indicate the location of code and data sets. Setting them once at the beginning of your data processing ensures that the right version of the code is executed, all the binaries will be found and that the data files are also correctly located.

Where do I find all those fantastic stats files FreeSurfer created for me?

- The stats output for each subject can be found in <subjid>/stats where subjid is the the name of one particular subject. To grab the stats files for several subjects to put them in spreadsheet-ready format, use the commands asegstats2table or aparcstats2table.

When mailing the FreeSurfer list about a problem, what information should I include?

- You should include the version of FreeSurfer you are using, the command line you tried to run, the error message you got either in the shell window or the recon-all.log, and the Operating System you are running FreeSurfer on. You can find out which version you are running by typing:

```
more $FREESURFER_HOME/build-stamp.txt
```

Why is spherical averaging better than current volume-based methods out there?

- Current volume-based registration methods cannot achieve high accuracy in aligning the cortical regions because of their high inter-subject variability. When we are only interested in finding correspondences between these areas (for example, in the case of functional studies), it is sufficient and also more accurate to register only the cortical areas with the spherical averaging method.

What is a limitation of this procedure?

- The alignment does not take into account the subcortical structures.

When you do all that crazy morph stuff, are you changing the data?

- When computing the deformation fields between a subject and another or an atlas, the data itself is not changed. When the deformation field is computed, however, it can be applied to the subject, which means resampling its scan(s) in the target coordinate space.

Do I have to remove every bit of skull, dura, etc. that I see in the brainmask? Why or why not?

- You only need to remove skull or dura if it affects the surfaces since we get our measurements from the surfaces.

Oh no! I made all these edits to a subject but now I want to rerun recon-all on the subject again with a new version of FreeSurfer. Will I lose all my work?

- If you have already made edits to a dataset, you can rerun it with a new version of

FreeSurfer and it will keep all of the edits you have already made as long as you run it on the existing dataset. In other words, you would just want to do "recon-all -all -s existing_subject".

Where do all those atlases come from that FreeSurfer uses?

- The different FreeSurfer atlases were generated from manually segmented data sets. Given each definition of the manual segmentation procedure and its labels, we constructed an atlas.

If a ran my subjects with version 4.0, can I run the rest with the newest version?

- For population studies and large scale comparisons, the best is to process all your data sets with the same version of FreeSurfer.

MORPHOMETRY PROTOCOLS (December 2011)

The following protocols are recommended for use with FreeSurfer. They have been tested on Siemens 1.5 T and 3 T MRI scanners (Sonata, Avanto, Allegra, Trio, TIM Trio). The 32-channel coil is recommended if available, otherwise the sequences will work with the 12-channel head matrix coil (also with 2x acceleration). 1 mm^3 isotropic resolution is recommended but 1.3 x 1 x 1.3 mm^3 is acceptable and can be used to save time or improve SNR.

MPRAGE

The following MPRAGE protocol was developed for good contrast between gray matter, white matter and CSF per unit of acquisition time. CSF appears dark and gray matter intensity is somewhere between CSF and white matter. Since the MPRAGE is not a steady-state sequence, different spatial frequencies have different contrasts, and gray matter intensity is not exactly midway between white matter and CSF for all spatial frequencies.

This protocol evolved together with FreeSurfer and is the basic acquisition protocol for brain morphometry studies. In cases where cortical thickness is the main interest, or cortical thickness and segmentation of other brain structures is required but time is limited, the MPRAGE should be used. If more time is available, the multiecho FLASH protocol is the preferred protocol for whole-brain segmentation. Listed below is the multiecho MPRAGE (MEMPR) protocol which has better B1 distortion properties than the single echo MPRAGE (as described in the section below on bandwidth matched imaging). The multiecho MPRAGE also contains T2* information that can be used to distinguish dura from cortical gray matter, adjacent tissues that are isointense in the standard MPRAGE protocol. If the MEMPRAGE sequence is not available, a single echo with a lower bandwidth of around 195 Hz/px is recommended.

Sequence: tfl_mgh_multiecho or tfl
Acquisition time: 6:03
Voxel size: 1.0 x 1.0 x 1.0 mm^3
Geometry: FoV 256 mm (256 x 256 matrix), 176 sagittal slices, slice thickness 1 mm, phase encoding anterior-posterior (readout superior-inferior) (3D encoding)
Timing: TR 2530 ms (3T)/2730 ms (1.5T), TI 1100 ms (3T)/1000 ms (1.5T), TE 1.64/3.5/5.36/7.22 ms, bandwidth 651 Hz/px for all echoes (bipolar readout trajectory)
RF: Non-selective IR, non-selective excitation at 7°
Acceleration: 2x GRAPPA (32 ref. lines)
(fast RF and gradient mode, no oversampling, no partial Fourier encoding, no fat suppression, no partial phase encoding, use “Prescan Normalize” but no other filters and avoid regular “Normalize”, use “Adaptive Combine”, increase image intensity (Fourier) scaling factor to 4.0 if possible, enable RMS averaging for MEMPR if available)
Exceptions: if multiple echo sequence is not available, choose bandwidth of 195 Hz/px and TE will be 3.31 ms. If acceleration is disabled and resolution is 1 mm^3 isotropic, increase TI to 1200 ms.

FLASH

The FLASH protocol is preferred for whole-brain segmentation where all brain structures are labeled by FreeSurfer. The acquisition requires more time – at least two separate acquisitions at two different flip angles are needed. However, the acquisition provides the data needed to calculate true quantitative T1 tissue parameters (measured in units of time) rather than the arbitrary T1-weighting that the MPRAGE provides. Proton density can also be calculated using two or more FLASH acquisitions. Listed below is the multiecho FLASH (MEF) protocol which delivers less distortion due to B0 inhomogeneities than single echo FLASH (as described in more detail in the following section). The multiecho FLASH sequence also provides T2* information, albeit quite noisy given the short TR. If this sequence is not available, a single echo with a lower bandwidth such as 130 Hz/px can be used.

Sequence: gre_mgh_multiecho or gre
Acquisition time: 8:28
Voxel size: 1.0 x 1.0 x 1.0 mm^3
Geometry: FoV 256 mm (256 x 256 matrix), 176 sagittal slices, slice thickness 1 mm, phase encoding anterior-posterior (readout superior-inferior) (3D encoding)
Timing: TR 20 ms, TE 1.85+n2.0 ms (n = 0,..,7), bandwidth 651 Hz/px for all echoes (bipolar readout trajectory)
RF: non-selective excitation at 30° and 5° (then 20°, then 3°)
Acceleration: 2x GRAPPA (32 ref. lines)
(fast RF and gradient mode, no oversampling, no partial Fourier encoding, no fat suppression, no partial phase encoding, no flow compensation, use “Prescan Normalize” but no other filters and avoid regular “Normalize”, use “Adaptive Combine”, increase image intensity (Fourier) scaling factor to 4.0 if possible)
Exceptions: if multiple echo sequence is not available, choose bandwidth of 130 Hz/px to 200 Hz/px and minimize TE.

Bandwidth matched imaging

For multispectral morphometry (where more than one contrast is used to assess structures), it is important that the images align properly so that voxels match across images of different contrasts. Although the amount of B0 related distortion is small, differences between structural scans with different bandwidths are nevertheless sufficient that the borders of structures and the cortical ribbon may not be properly aligned everywhere especially in areas of higher susceptibility change.

To solve the differential distortion problem, we assembled a set of high bandwidth protocols. The higher bandwidth results in lower SNR but the SNR is recovered by acquiring and combining the multiple echoes. The chosen bandwidth of 651 Hz/px is also convenient for the T2-SPACE (T2 weighted) sequence, therefore all of these sequences can be matched to a high bandwidth and residual distortions are matched.

Listed below is the T2-SPACE protocol to accompany the above-listed protocol. Together with the MEMPR and MEF, this protocol provides a T1-weighted volume, T2-weighted volume and the data needed to estimate quantitative PD, T1 and approximate T2*.

Sequence: tse_vfl
Acquisition time: 5:00
Voxel size: 1.0 x 1.0 x 1.0 mm^3
Geometry: FoV 256 mm (256 x 256 matrix), FoV phase 79.7%, 176 sagittal slices, slice thickness 1 mm, phase encoding anterior-posterior (readout superior-inferior) (3D encoding)
Timing: TR 3390 ms, TE 388 ms, bandwidth 651 Hz/px, turbo factor 115, slice turbo factor 2, echo train duration 769, echo spacing will be 3.36 ms
RF: non-selective excitation (flip angle mode “T2 var”)
Acceleration: 2x GRAPPA (24 ref. lines)
(normal RF and fast gradient mode, no oversampling, no partial Fourier encoding, no partial phase encoding, no flow compensation, use “Prescan Normalize” and avoid regular “Normalize”, use “Adaptive Combine”, different Siemens software baselines may vary w.r.t. timing parameters and exact FoV phase)

For 1.3 x 1 x 1.3 mm^3 resolution, change “Phase resolution” to 75%, slice thickness to 1.33 mm and number of slices to 128 for all of the above sequences (for T2-SPACE the phase resolution may not be exactly 75%). Since this decreases acquisition time, parallel acceleration may be switched off to further increase SNR.

Custom multiecho sequences for Siemens scanners are available from the Martinos Center. The sequences and protocols are provided for free, but an indemnification document must be signed.

MPRAGE equivalent protocol for Philips and GE scanners

The following protocols were developed by the INTRuST NLC[1] for Philips and GE 3 T scanners to match the Siemens recommended T1 structural (MPRAGE) protocol for morphometry.

GE T1 structural protocol

Sequence: SPGR-BRAVO (IR-FSPGR with ASSET)
Acquisition time: 5:15
Voxel size: 1.0 x 1.0 x 1.0 mm^3
Geometry: FoV 25.6 cm (256 x 256 matrix), 176 sagittal slices, slice thickness 1 mm, (3D encoding)
Timing: TR min (9150 ms), TI 600 ms, TE min (3.7 ms), bandwidth 25 kHz (195 Hz/px)
RF: flip angle 10°
Acceleration: 2x Asset

Philips T1 structural protocol

Sequence: T1W_3D_TFE_SENSE
Acquisition time: 5:13
Voxel size: 1.0 x 1.0 x 1.0 mm^3
Geometry: FoV 256 mm (256 x 256 matrix), 176 sagittal slices, slice thickness 1 mm, (3D encoding)
Timing: TR shortest (7600 ms), TI 1100 ms, TE shortest (3.5 ms), bandwidth 191.5 Hz/px
RF: flip angle 7°
Acceleration: 2x SENSE

MPRAGE variants from MGH

The MEMPR and slightly modified MEF sequences are available from MGH by C2P agreement. The legal process, although straightforward in principle, may take a couple of months. Email: André van der Kouwe (andre at nmr.mgh.harvard.edu).

The motion corrected MEMPR with vNavs is available from Siemens as a works-in-progress package (WiP 711) through your local Siemens representative (created by M. Dylan Tisdall, MGH, and Himanshu Bhat, Siemens).

OTHER EXAMPLE PROTOCOLS

This document and example generic morphometry, DTI and fMRI protocols for Siemens scanners are available at http://www.nmr.mgh.harvard.edu/~andre/.

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[1] INTRUST (Posttraumatic Stress Disorder and Traumatic Brain Injury Clinical Consortium) NLC (Neuroimaging Leadership Core): Shenton, Kikinis, Rosen (PIs), Helmer, van der Kouwe, Kubicki, Pasternak (http://intrust.spl.harvard.edu)