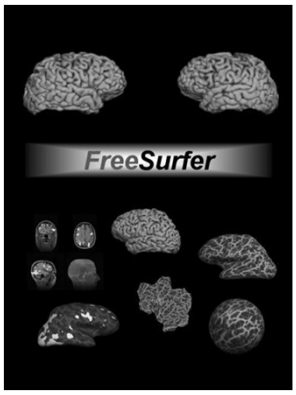
Multimodal Integration



Slides prepared by:
Douglas Greve

MASSACHUSETTS GENERAL HOSPITAL

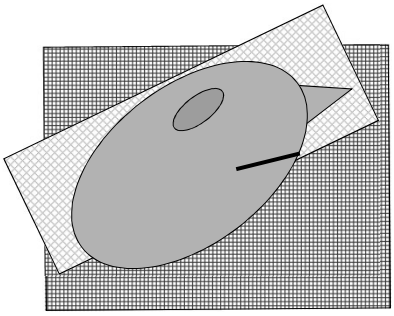
Overview

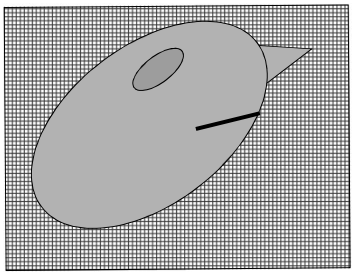
- Affine transformations
- Registration, Automatic and Manual
- fMRI Integration
  - fMRI Analysis Intro
  - Registration
  - Viewing on Volume and Surface
  - ROI analyses
  - Surface-based group analysis

Theory of Affine Spatial Transforms

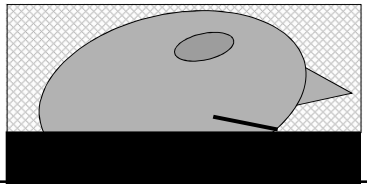
Anatomical (1x1x1.1mm, 256x256x128, Sag)

Scanner Acquisition





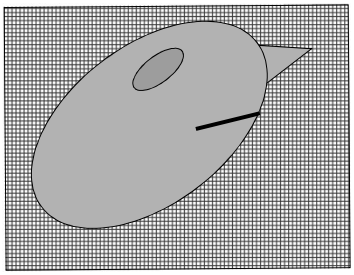
fMRI/DTI/PET (3x3x5mm, 64x64x30, Axial)



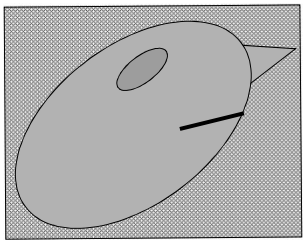
3

Theory of Affine Spatial Transforms

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



Conformed Anatomical Space
1x1x1mm, 256x256x256, Cor

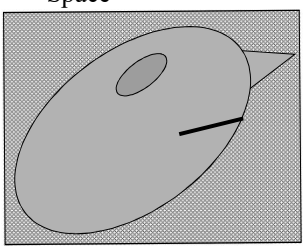


"Anatomical Space"
orig.mgz
Surfaces
Parcellations
Segmentations

4

Theory of Affine Spatial Transforms

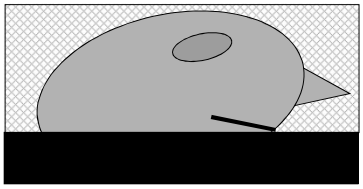
"Anatomical Space"



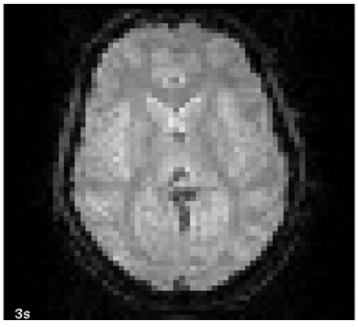
Conformed Anatomical Space
1x1x1mm, 256x256x256, Cor

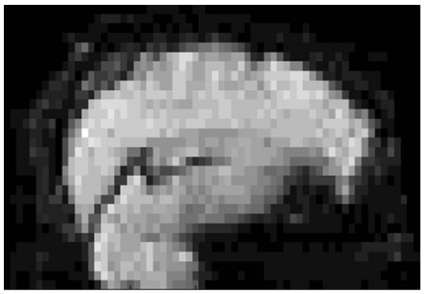
???

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



fMRI/DTI/PET
Have Multiple Frames/Time Points





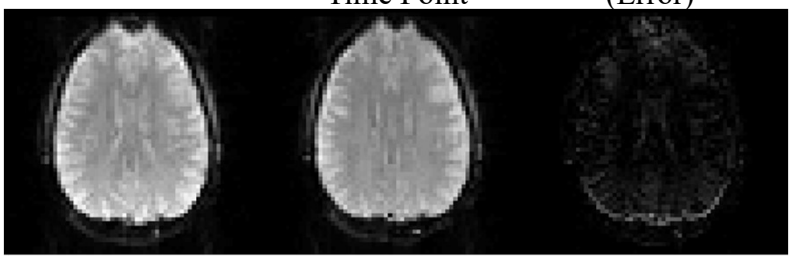
Movement!

fMRI/DTI/PET Motion Correction

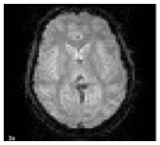
Template
Target
Reference

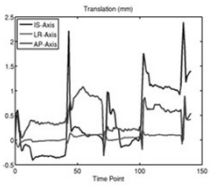
Input
Time Point

Difference
(Error)



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

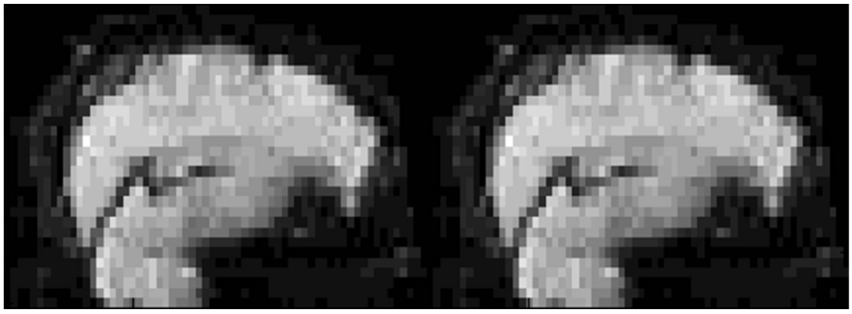




Motion Correction

Raw

Corrected

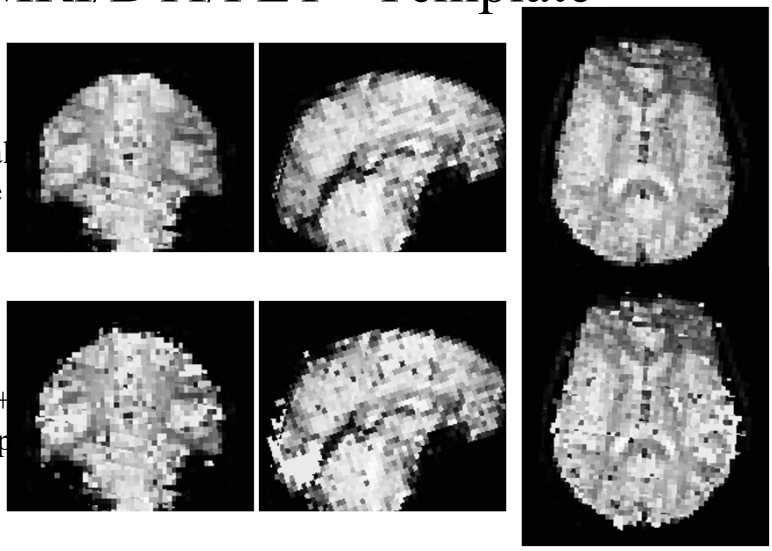


- Motion correction reduces motion
- All frames/time points should be in alignment
- Not perfect

fMRI/DTI/PET "Template"

Functional Template

Template+ fMRI Map

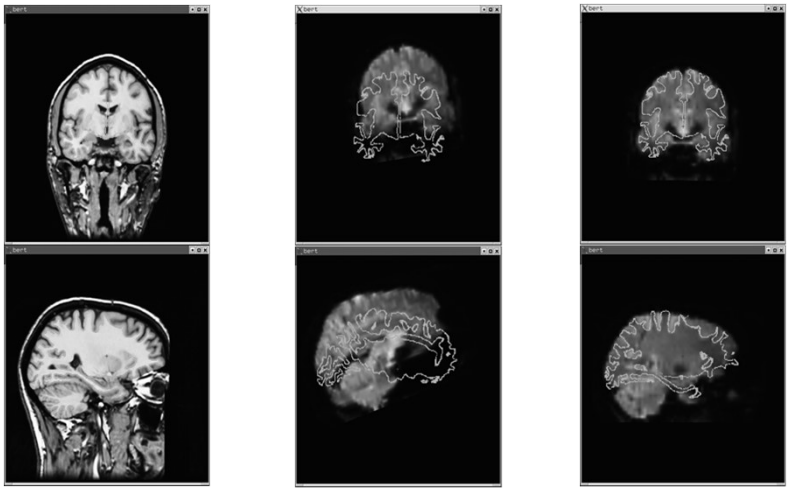


Usually template/reference/target used for motion correction

Registration

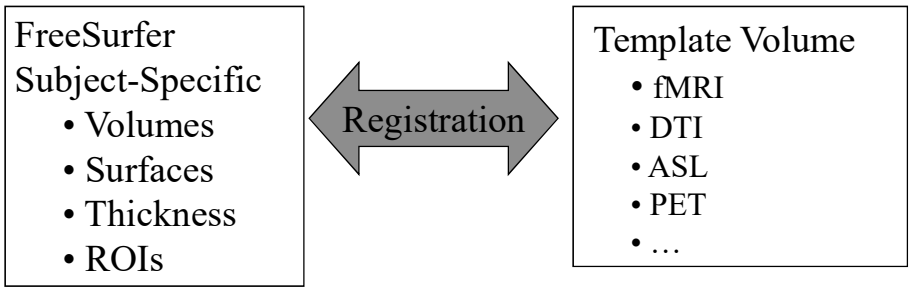
FreeSurfer Anatomical (orig)

Template



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

FreeSurfer Registration and Template Volume



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

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)
- Also source / target file information
- Coordinate system not easy to explain

```
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
```



```
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
```

Automatic Registration

```
bbregister \
  –-s bert \
  –-mov mmtemplate.nii \
  --bold \
  --init-fsl \
  --lta register.lta
```

→ Command name
→ FreeSurfer subject name
→ Multimodal template volume
→ Multimodal contrast
→ Initialize with FSL-FLIRT
→ Output registration file

- BB = Boundary-based, about 5 min.
- Registers template to conformed anatomical of given subject (bert)
- Registration is initialized with FSL-FLIRT
- 6 DOF
- Initialization also with --init-spm and --init-header
- About 5 min

Manual Registration

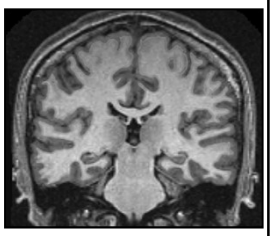
```
freeview -v template.nii\
        $SUBJECTS_DIR/fbirn-anat-101.v4/mri/orig.mgz:visible=0\
    -f  $SUBJECTS_DIR/fbirn-anat-101.v4/surf/lh.white:edgecolor=green\
        $SUBJECTS_DIR/fbirn-anat-101.v4/surf/rh.white:edgecolor=green\
    -viewport coronal
```

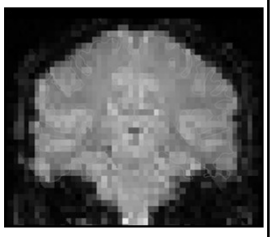
- Turn the orig volume on/off or change opacity of top volume to see current quality of alignment
- Select volume to move, then “Tools” and “Transform Volume”
- Explore the Translate and Rotate tabs
- To restart the process, use “Restore to Original”
- Use the “Save Reg” button to save the registration 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

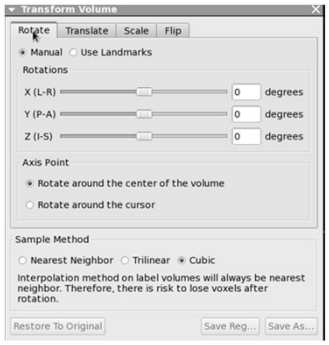
freeview --help

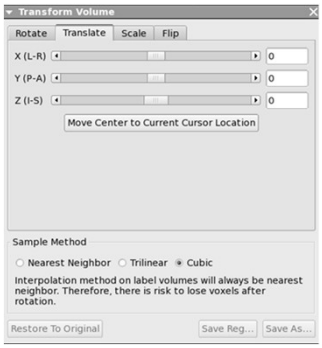
Manual Registration

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





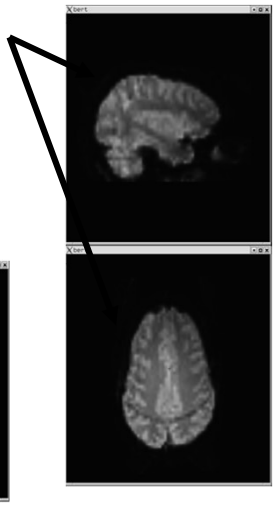


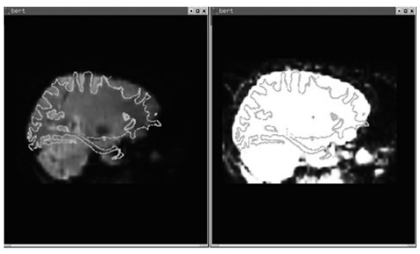


freeview --help

Tips

- 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





Command-line Tools

Automatic Registration:

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

} FreeSurfer Scripts

Manual Registration:

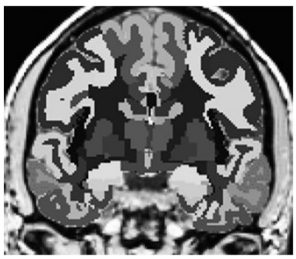
- freeview --help

Transformations:

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

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

DTI Analysis Overview

- Motion/Eddy Current Correction (MC Template)
  - Usually a low-b volume
  - Use for registration template

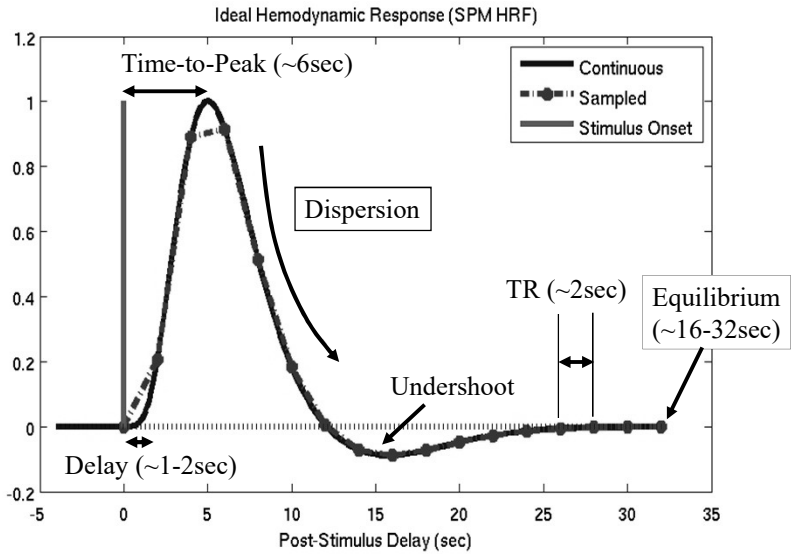
```
bbregister --mov mctemplate.nii --s subject --init-fsl --lta register.lta
freeview -v mctemplate.nii:reg=register.lta -f $SUBJECTS_DIR/subject/surf/?h.white
```

- First-Level (Individual) Analysis
  - Fit Tensor Model
  - Maps: FA (0-1), ADC, Eigenvectors, etc
  - All in alignment with MC Template!!!!

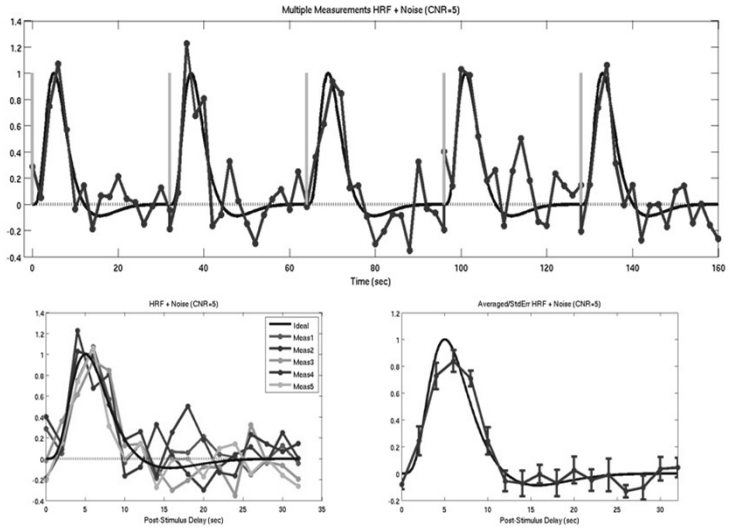
fMRI Integration

- 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)

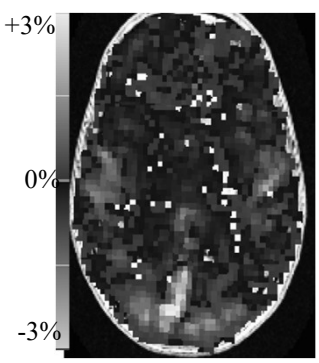


Multiple Presentations/Averaging



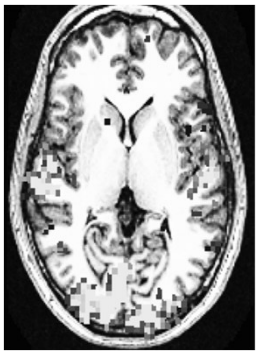
Individual Output: HRF Amp, HRF Var, p/z/t/F

Statistical Parametric Map (SPM)



Contrast Amplitude
CON, COPE, CES

Contrast Amplitude
Variance
(Error Bars)
VARCOPE, CESVAR



Significance
t-Map (p,z,F)
(Thresholded p<.01)
sig=-log10(p)

"Massive Univariate Analysis"
-- Analyze each voxel separately

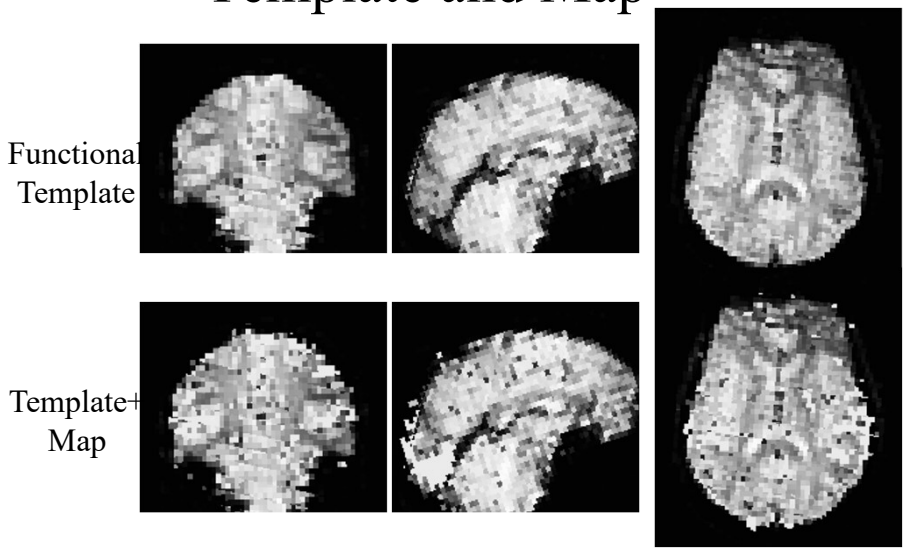
fMRI Preprocessing Overview

- Motion Correction (MC Template)
  - Use for registration template
  - 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 nonlinear resampling to Talairach/MNI space
- Do not spatially smooth (3D)

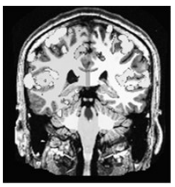
fMRI Analysis Overview

- 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!!!!

Template 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

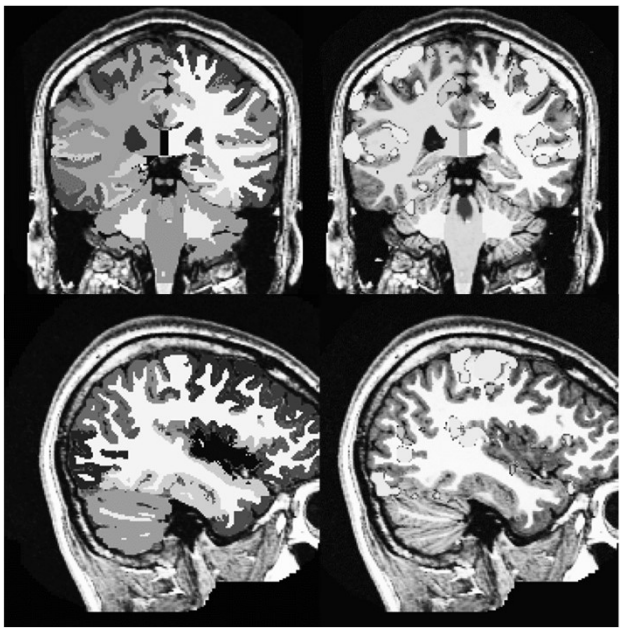
```
freeview -v $SUBJECTS_DIR/fbirn-anat-101.v4/mri/orig.mgz \
            $SUBJECTS_DIR/fbirn-anat-101.v4/mri/aparc+aseg.mgz:colormap=lut:opacity=.3 \
            sig.nii:colormap=heat:heatscale=2,3.0,4:reg=register.lta
```

sig.nii – significance map in native functional space. could have been z, t, or F map as well.

register.lta – FreeSurfer registration file

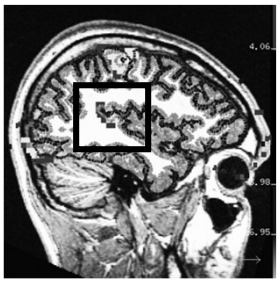
aparc+aseg – display aparc+aseg.mgz. You can load this from the interface, too.

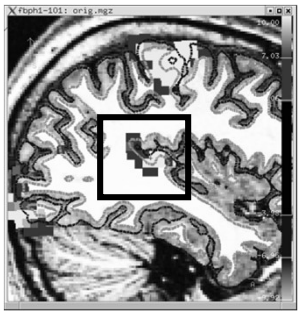
Volume Viewing

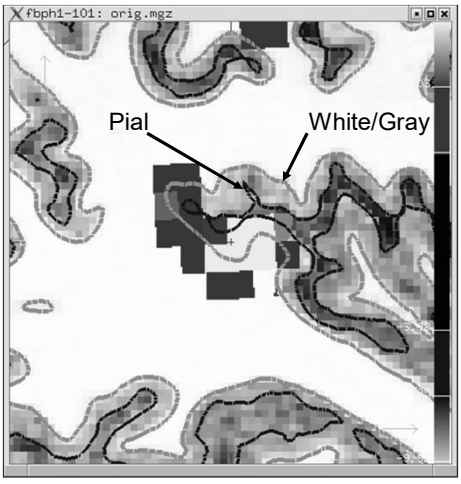


- Red/Yellow +
- Blue/Cyan -
- Seg Opacity
- ROI Average
- ROI Count

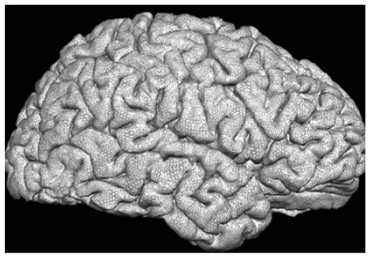
Sampling onto the Surface

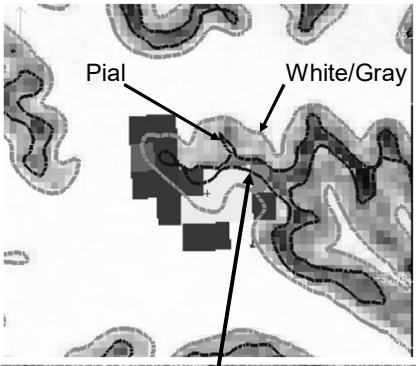






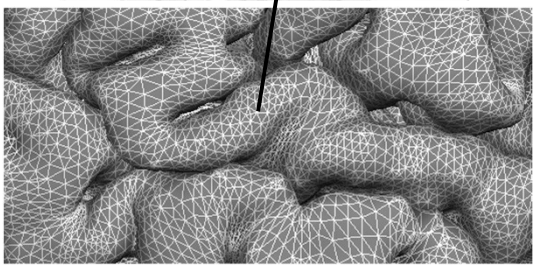
Sampling onto the Surface



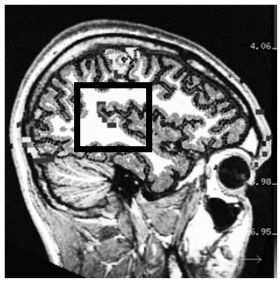


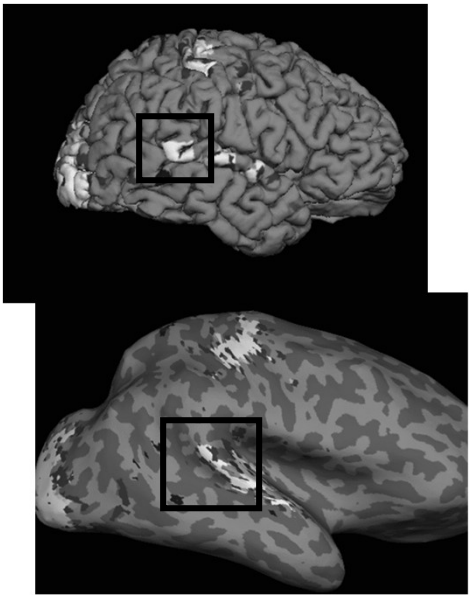
- White/Gray
- Pial
- Half Way
- Average

Projection Fraction
--projfrac 0.5

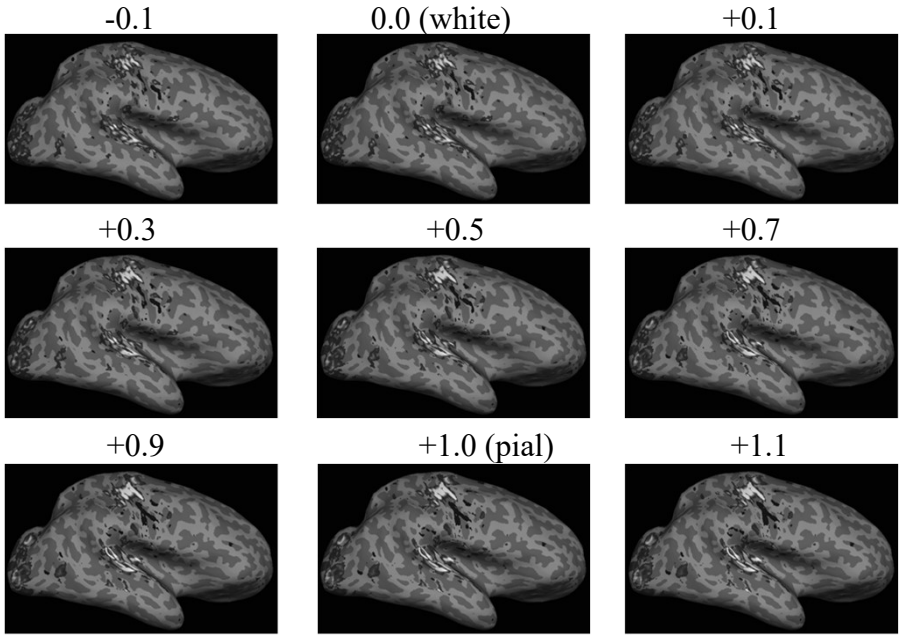


Sampling on the Surface





Sampling on the Surface: Projection Fraction



Surface Viewing

Resample HRF Contrast Significance to left hemisphere

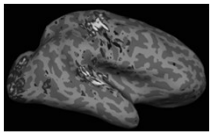
```
mri_vol2surf \
  --mov sig.nii \          → map in native functional space
  --reg register.lta \     → FreeSurfer registration file
  --hemi lh \              → hemisphere
  --projfrac 0.5 \         → projection fraction (half)
  --o lh.sig.mgh           → output (Nvertices-x-1 mgh format)
```

Note similarity to bbregister command!

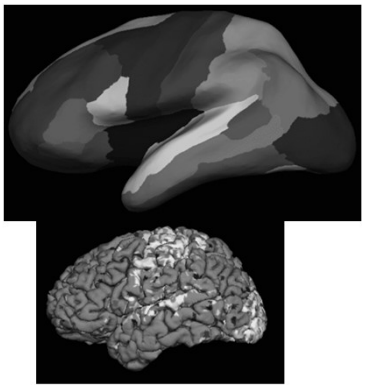
Load HRF Contrast Significance as overlay

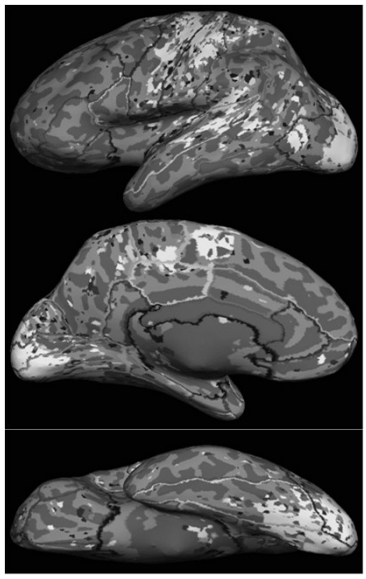
```
freeview -f $SUBJECTS_DIRsubject/surf/lh.inflated:annot=aparc.annot:overlay=lh.sig.mgh:overlay_threshold=2,5 \
         -viewport 3d

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 …

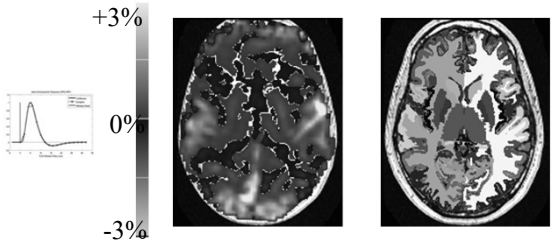
```
mris_fwhm --i lh.fsaverage.ces.mgh --fwhm 10 \
  --o lh.fsaverage.ces.sm10.mgh --cortex

mri_glmfit --surf fsaverage lh –cortex \
  --y lh.fsaverage.ces.sm10.mgh ...
```

ROI fMRI Analyses:

- HRF Amplitude
  - Full Anatomical ROI
  - Functionally Constrained ROI
- Volume

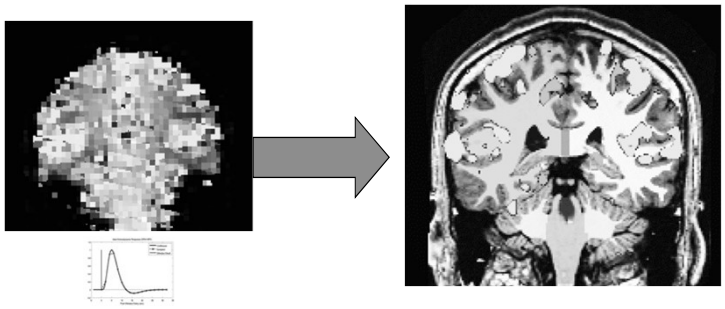
Average HRF within a Functionally Active area inside of an Anatomical ROI



Contrast Amplitude

Eg, average functional HRF amplitudes from voxels inside of superior temporal gyrus (light blue) regardless of significance

Step 1. Resample HRF Contrast to anatomical space

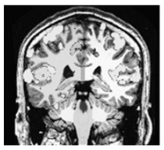


```
mri_vol2vol \                → Command name
  --mov ces.nii \            → HRF map in functional space
  --reg register.lta \       → FreeSurfer Registration File
  --interp nearest \         → Nearest neighbor interpolation
  --fstarg \                 → Specify anatomical output space
  --o ces.anat.mgh           → Output file in anatomical space
```

Note similarity to bbregister and mri_vol2surf commands!

Step 2: Average HRF Contrast within ROIs

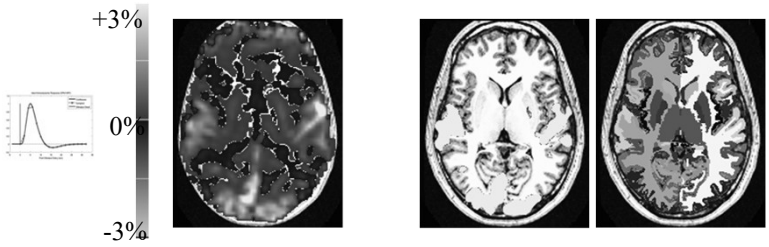
```
mri_segstats
  --seg $SUBJECTS_DIR/subject/mri/aseg.mgz
  --ctab $FREESURFER_HOME/FreeSurferColorLUT.txt
  --i ces.anat.mgh
  --sum ces.aseg.stats
```



Notes:
--seg is the segmentation (eg, 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



Contrast Amplitude

Significance (p<.01)

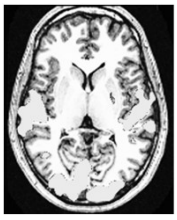
Eg, average functional HRF amplitudes from voxels inside of superior temporal gyrus (light blue) for voxels that have

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)

Average HRF only within the Functionally Active Area of an Anatomical ROI, Count Voxels above threshold in each ROI

Resample HRF Contrast Significance to anatomical space

```
mri_vol2vol \
  --mov sig.nii \
  --reg register.lta \
  --interp nearest \
  --fstarg \
  --o sig.anat.mgh
```



Average HRF Contrast within functionally constrained ROIs

```
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
```

Average HRF only within the Functionally Active Area of an Anatomical ROI, Count Voxels above threshold in each 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 volume above threshold (may be 0)
- Sign is important for Average!
  - abs, pos, or neg
  - pos will always result in positive HRF average
  - neg will always result in negative HRF average
  - abs ????
- Careful to avoid circularity
  - Can use a different contrast to mask

Summary

- Multi/Cross-modal map (HRF Amplitude, FA)
- Multimodal Integration requires a Template
- A 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 MC template
- Volume and Intensity ROI Analyses
  - Functionally-constrained ROI

Tutorial

1. Registration – manual and automatic registration
2. fMRI Integration (Sensorimotor Paradigm)
    1. Individual
        1. Volume view sig
        2. Surface view sig
        3. ROI analysis with and without functional constraint
    2. Group
        1. mris_preproc
        2. ROI analysis (asegstats2table)

FreeSurfer Registration Matrix

- 4x4 Matrix
- As many as 12 DOF (usually 6)
- Simple Text file
- Coordinate system not easy to explain

```
mgh-02407836-v2
3.437500
5.000000
0.150000
9.999985e-01 -1.428481e-03 -8.293565e-04 5.281680e-01
4.641568e-04 -2.388080e-01 9.710670e-01 -4.041043e+01
1.585159e-03 9.710652e-01 2.388064e-01 -1.376212e+00
0 0 0 1
round
```


FreeSurfer Registration Matrix

- 4x4 Matrix
- As many as 12 DOF (usually 6)
- Simple Text file
- Coordinate system not easy to explain

```
mgh-02407836-v2   → FreeSurfer subject name
3.437500          → Functional In-plane resolution mm
5.000000          → Functional Between-plane resolution mm
0.150000          → Intensity (for visualization)
9.999985e-01 -1.428481e-03 -8.293565e-04 5.281680e-01
4.641568e-04 -2.388080e-01 9.710670e-01 -4.041043e+01
1.585159e-03 9.710652e-01 2.388064e-01 -1.376212e+00
0 0 0 1
round             → Legacy
```

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
  –-reg register.dat            → Output registration file
```

- BB = Boundary-based, about 5 min.
- Registers template to conformed anatomical of given subject (bert)
- Registration is initialized with FSL-FLIRT
- 6 DOF
- Initialization also with --init-spm and --init-header
- About 5 min

Manual Registration

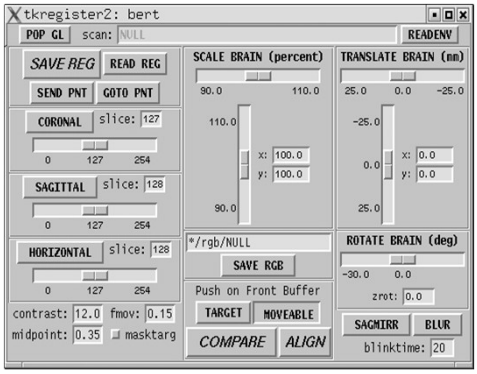
```
tkregister2 \                   → Command name
  –-mov mmtemplate.nii \        → Multimodal template volume
  –-reg register.dat \          → registration file
  --surfs                       → Display white surf
```

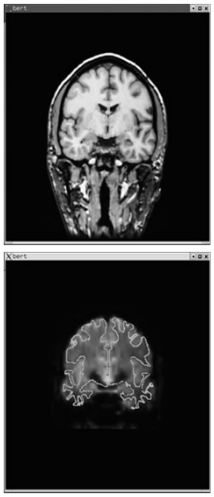
- Note similarity to bbregister command
- Subject not needed (already in register.dat file)

tkregister2 --help

Manual Registration

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





tkregister2 --help

DTI Analysis Overview

- Motion/Eddy Current Correction (MC Template)
  - Usually a low-b volume
  - Use for registration template
  - bbregister --mov mctemplate.nii --s subject --init-fsl --reg register.dat
  - tkregister2 --mov mctemplate.nii --reg register.dat --surf
- First-Level (Individual) Analysis
  - Fit Tensor Model
  - Maps: FA (0-1), ADC, Eigenvectors, etc
  - All in alignment with MC Template!!!!

Command-line Tools

Automatic Registration:

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

} FreeSurfer Scripts

Manual Registration:

- tkregister2 --help

Transformations:

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

fMRI Preprocessing Overview

- Motion Correction (MC Template)
  - Use for registration template
  - bbregister --mov mctemplate.nii --s subject --init-fsl --reg register.dat
  - tkregister2 --mov mctemplate.nii --reg register.dat --surf
- Do not use nonlinear resampling to Talairach/MNI space
- Do not spatially smooth (3D)