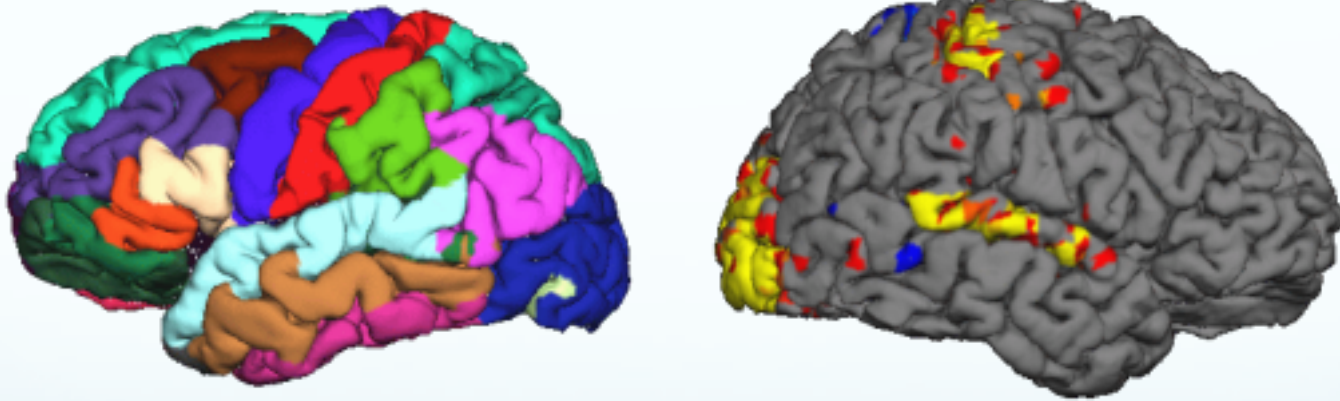


- [freesurfer.net](http://freesurfer.net)

# Multimodal Integration

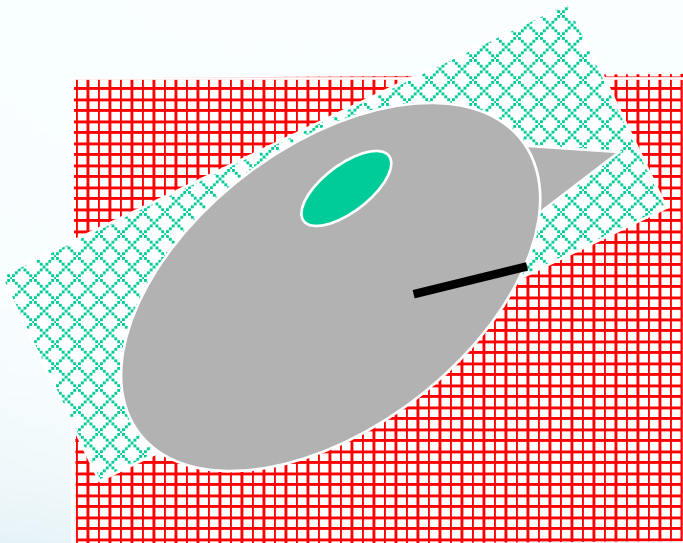


# Outline

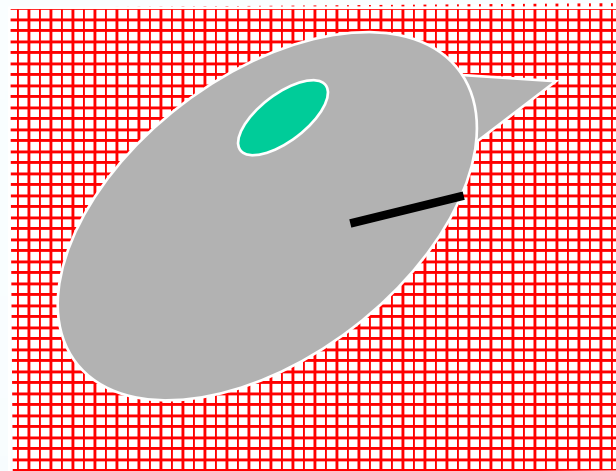
- Spatial Transformation
- Motion Correction
- Registration, Automatic and Manual
- MultiModal Integration
  - DTI Integration
  - fMRI Integration
  - Viewing on Volume and Surface
  - ROI analyses
  - Surface-based group analysis

# Spatial Transformations

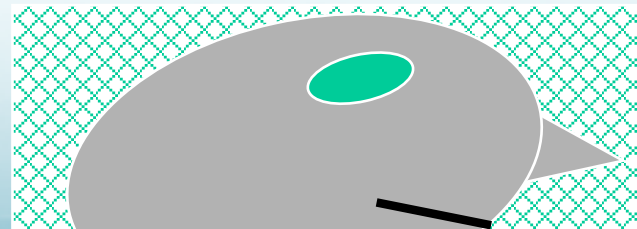
Scanner Acquisition



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

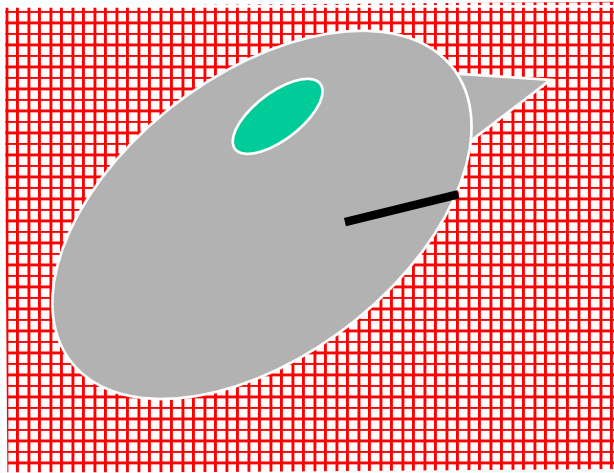


fMRI/DTI/PET  
(3x3x5mm, 64x64x30, Axial)

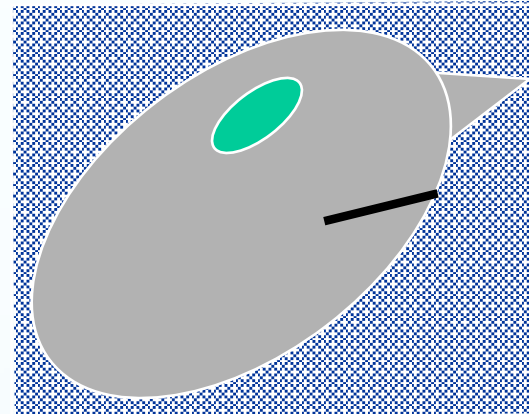
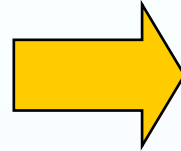


# Spatial Transformations

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



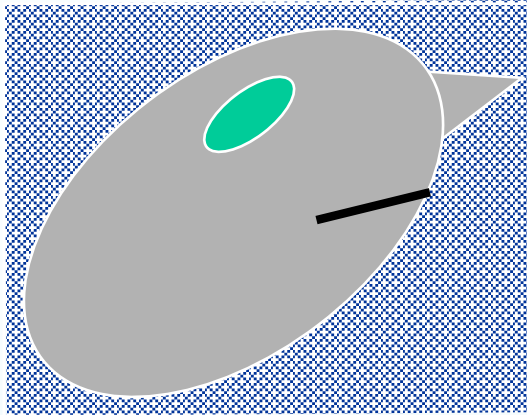
Conformed Anatomical Space  
1x1x1mm, 256x256x256, Cor



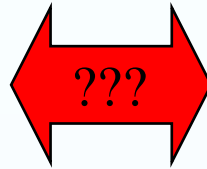
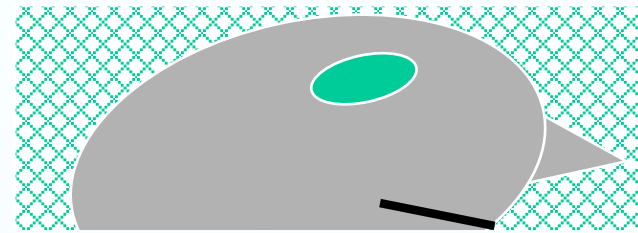
“Anatomical Space”  
orig.mgz  
Surfaces  
Parcellations  
Segmentations

# Spatial Transformations

“Anatomical Space”



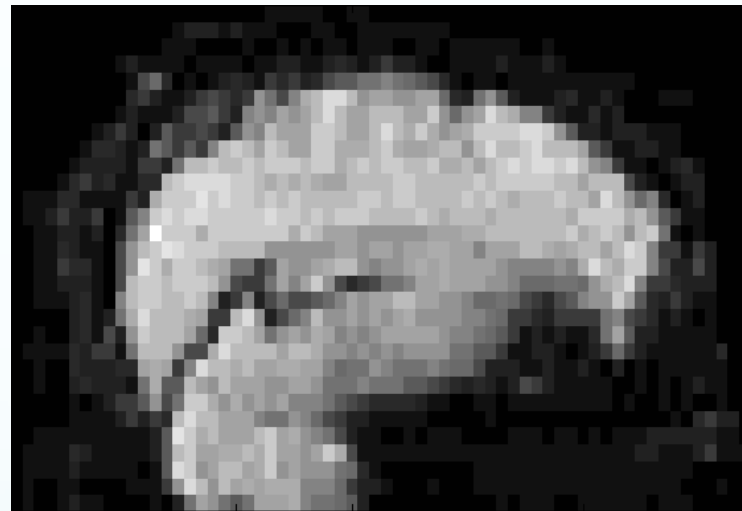
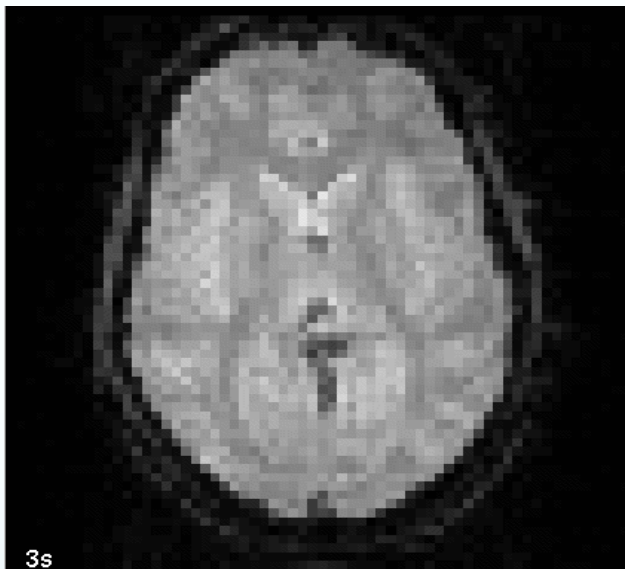
Native fMRI/DTI/PET Space  
3x3x5mm, 64x64x30, Axial



Conformed Anatomical Space  
1x1x1mm, 256x256x256, Cor

# fMRI/DTI/PET

Have Multiple Frames/Time Points



Movement!

# Motion Correction

Template

Target

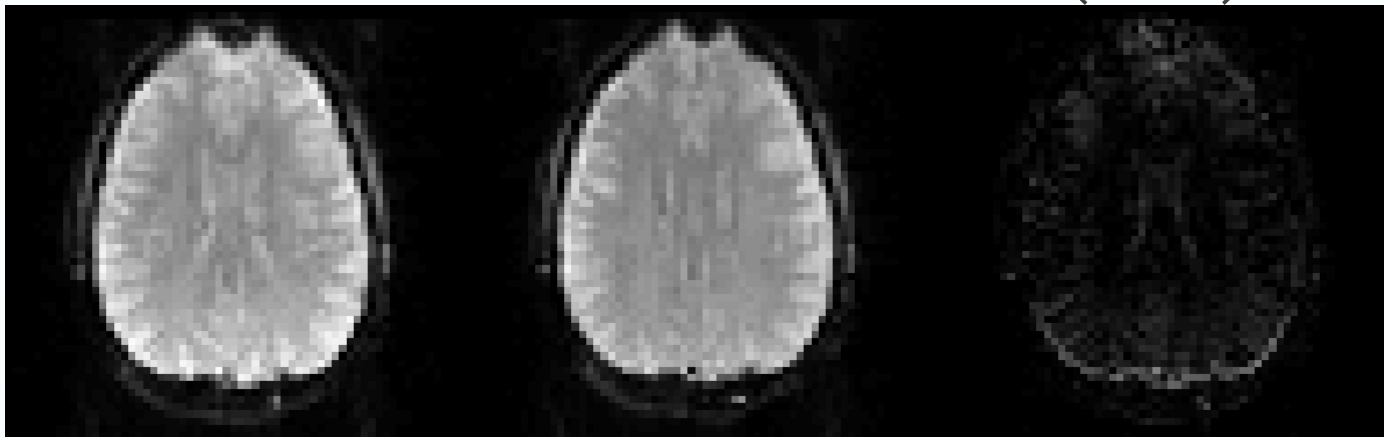
Reference

Input

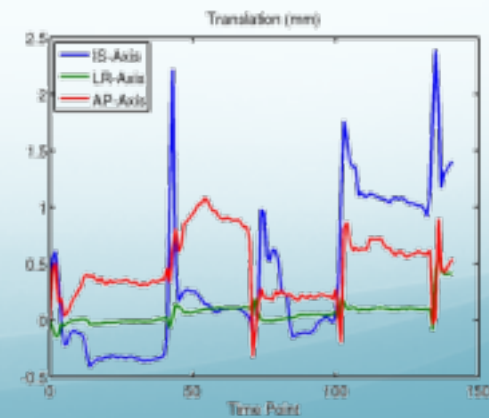
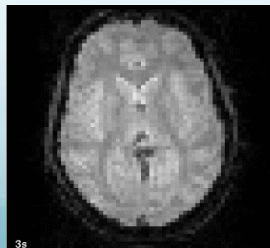
Time Point

Difference

(Error)



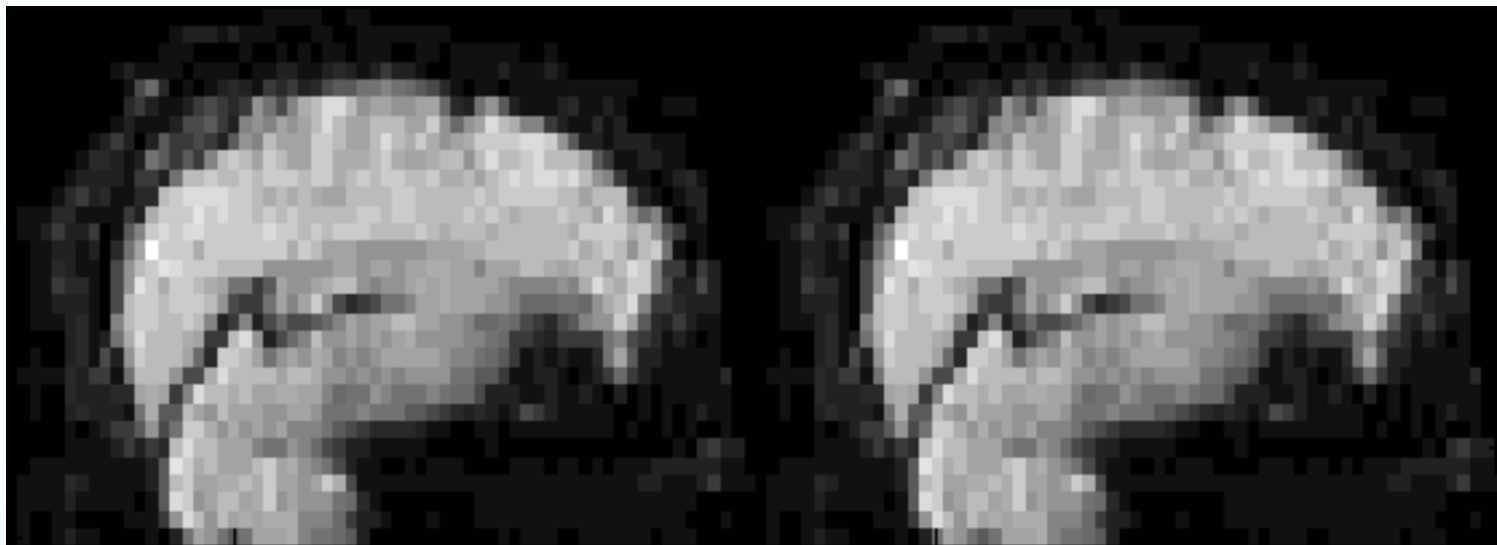
- Adjust translation and rotation of input time point to reduce absolute difference.



# Motion Correction

Raw

Corrected

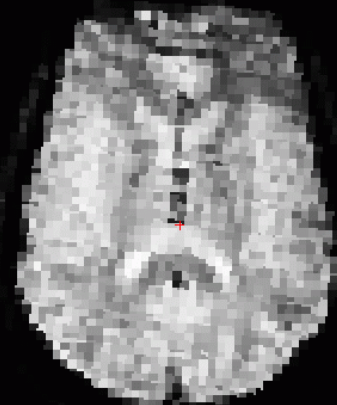
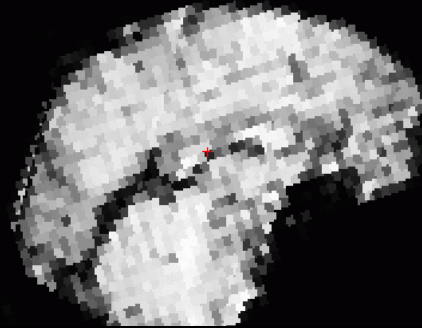
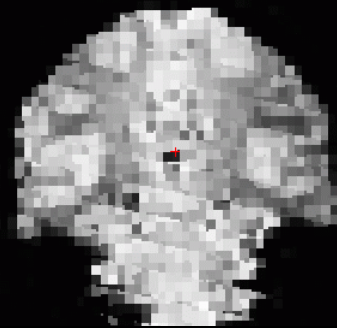


- Motion correction reduces motion
- All frames/time points should be in alignment
- Not perfect

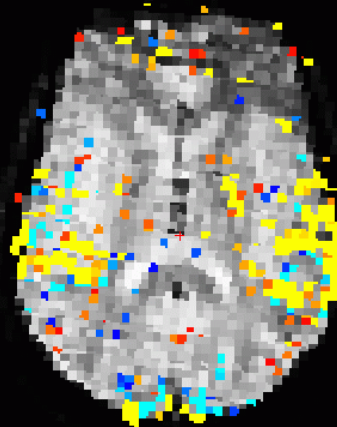
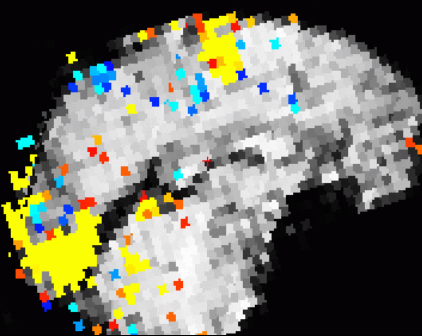
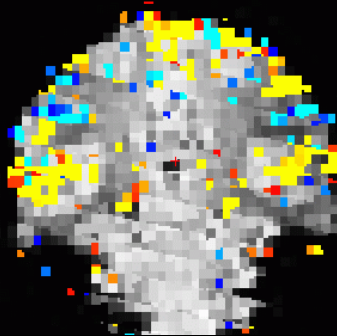


# fMRI/DTI/PET “Reference”

Functional  
Template



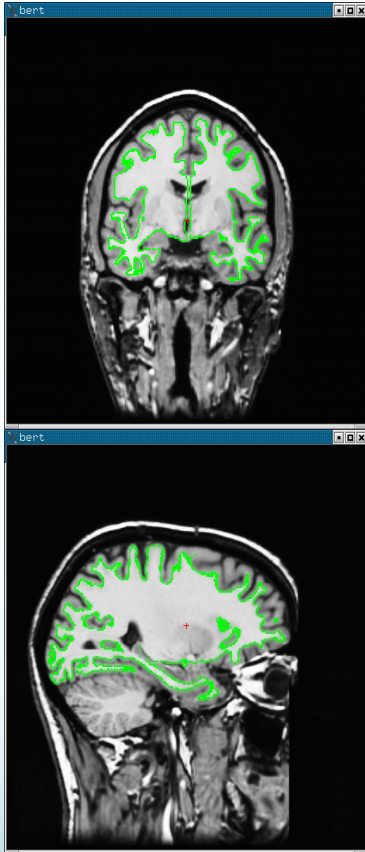
Template+  
fMRI Map



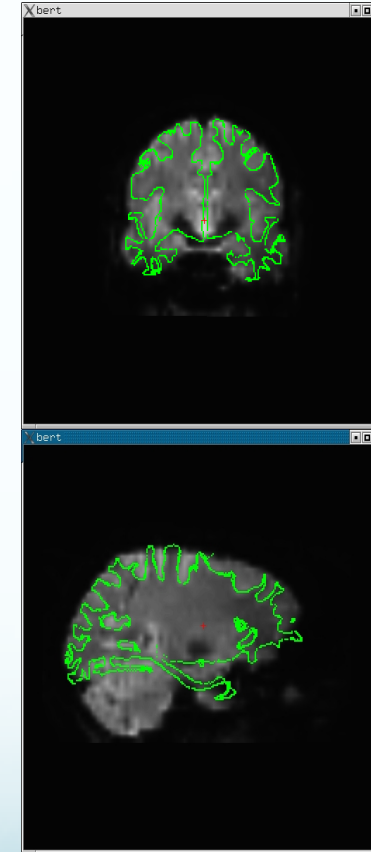
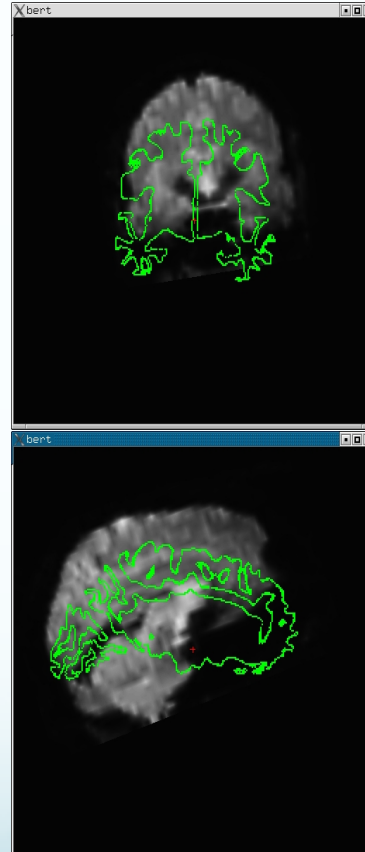
Usually template/reference/target used for motion correction

# Registration

FreeSurfer Anatomical (orig)



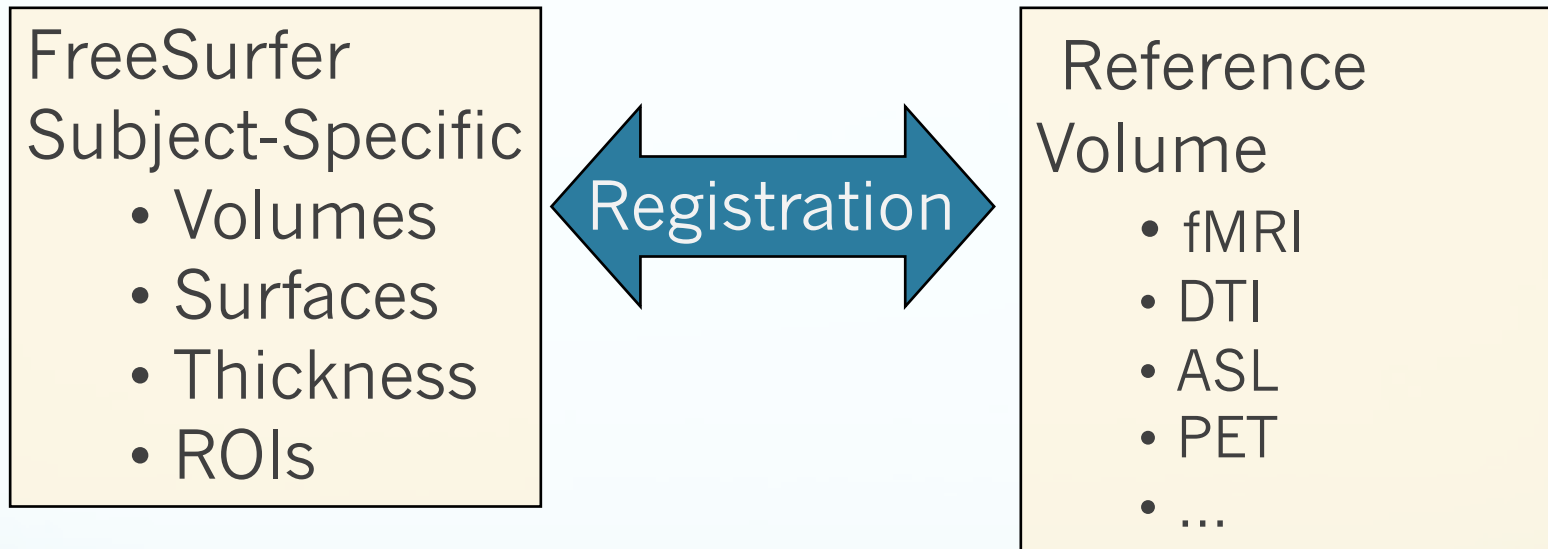
Template



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



### Reference/Template Volume:

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

# Automatic Registration

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

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

# Manual Registration

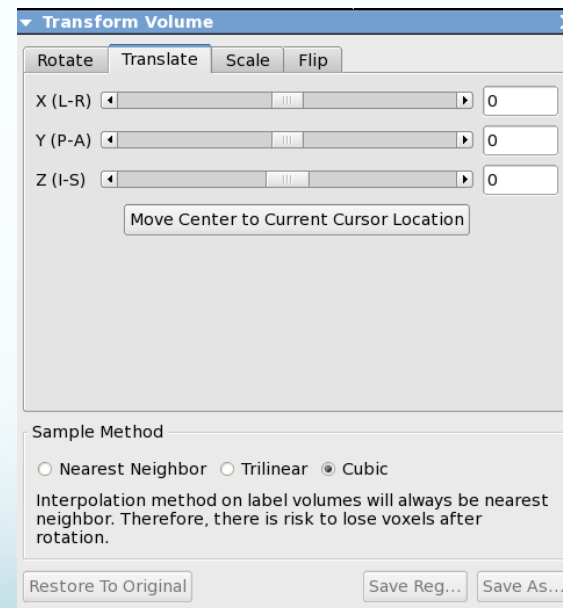
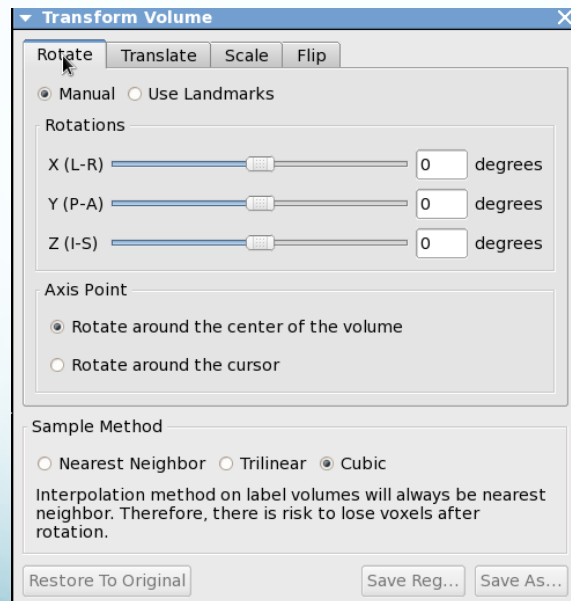
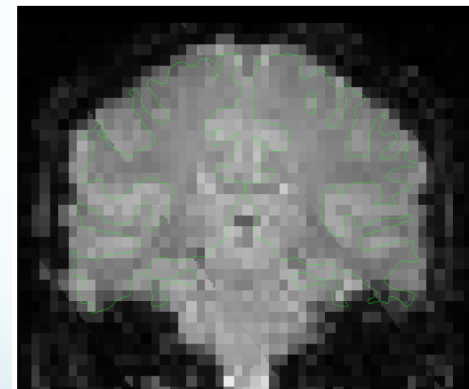
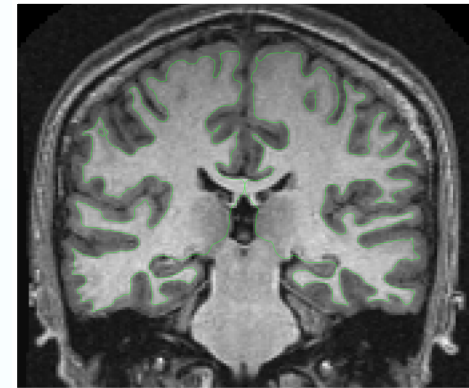
```
freeview -v template.nii \  
    $SUBJECTS_DIR/fbirn-anat-101.v4/mri/orig.mgz:visible=0 \  
-f $SUBJECTS_DIR/fbirn-anat-101.v4/surf/lh.white:edgecolor=green \  
    $SUBJECTS_DIR/fbirn-anat-101.v4/surf/rh.white:edgecolor=green \  
-viewport coronal
```

- 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

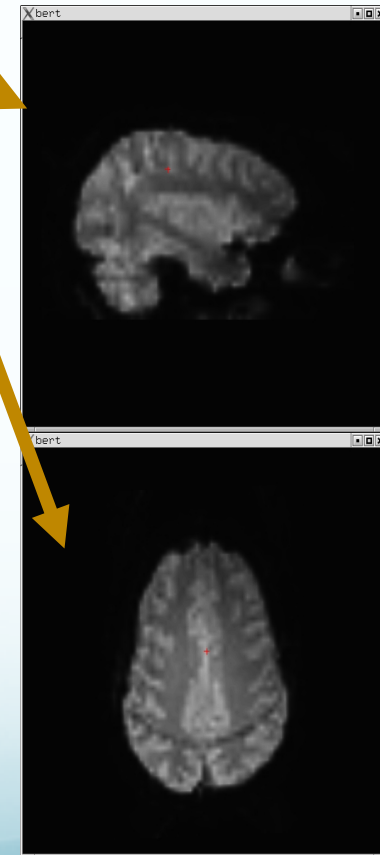
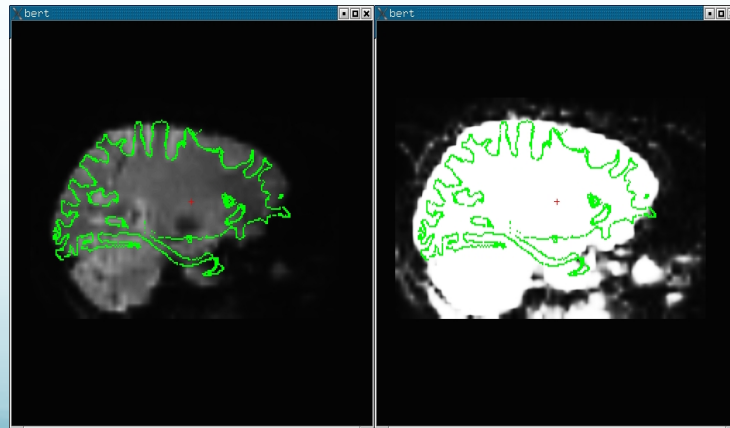
- Visually inspect registration
- Manually edit registration (6 DOF)
- cf Manual Talairach registration
- Green line is white surface



freeview --help

# 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:

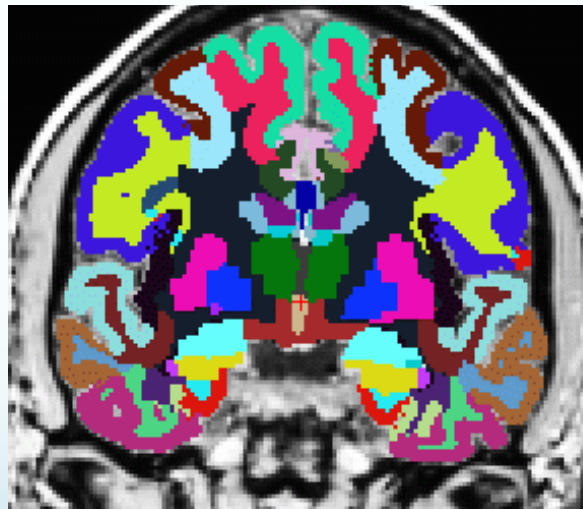
- `freeview --help`

## Transformations:

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

# 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 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
```

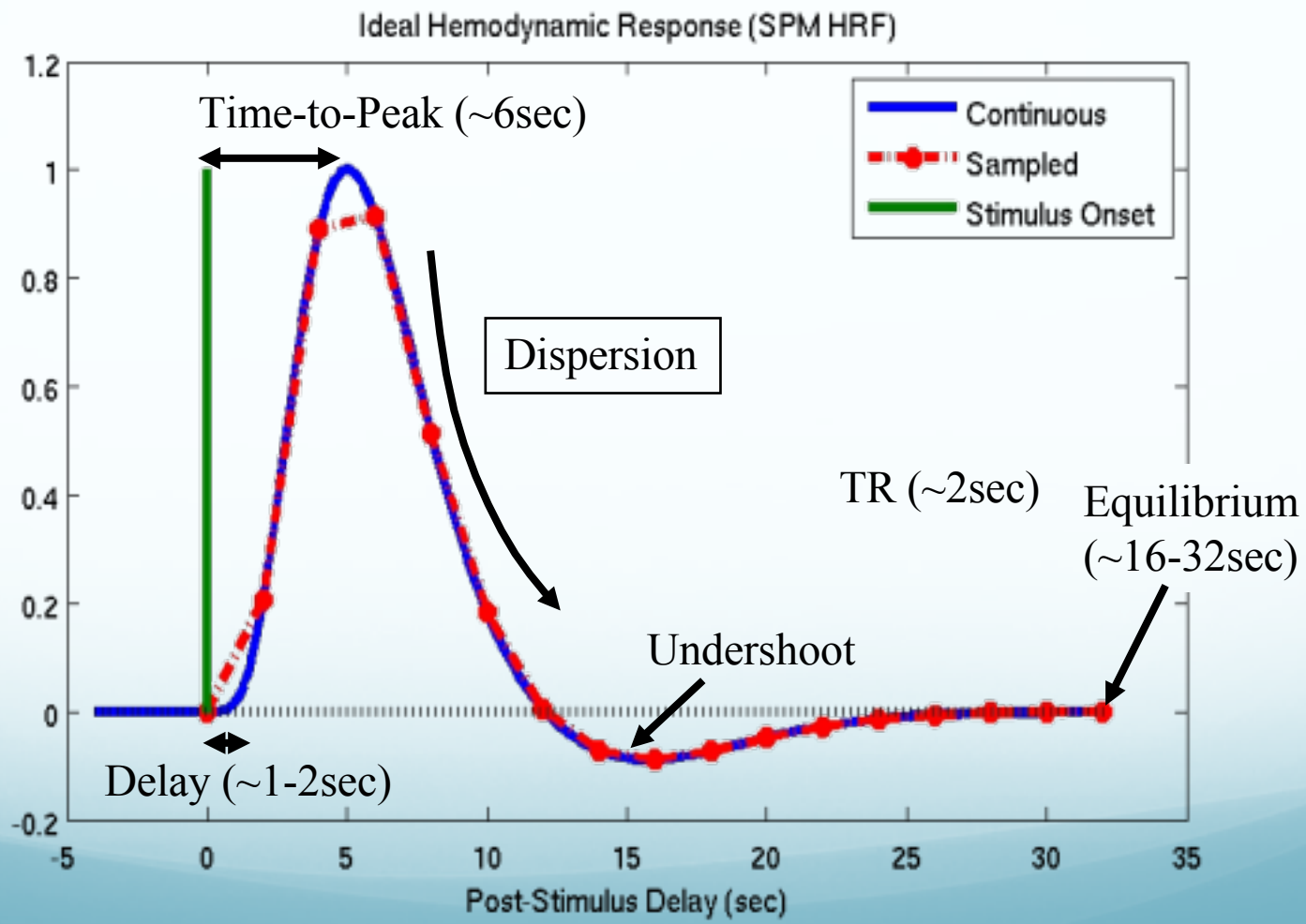
```
freeview -v mctemplate.nii:reg=register.lta -f $SUBJECTS_DIR/subject/surf/?h.white
```

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

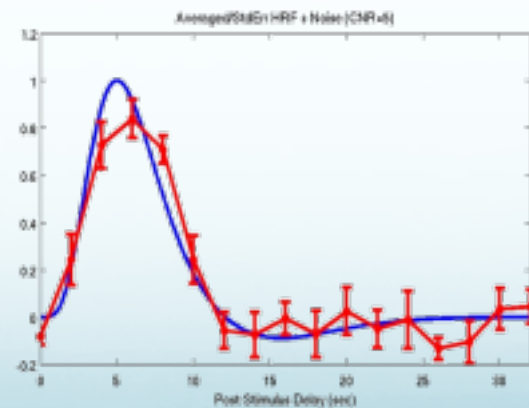
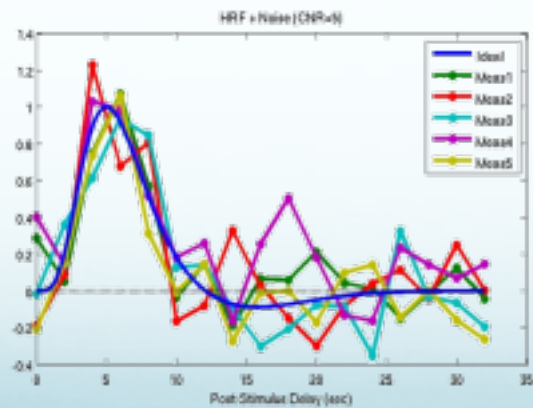
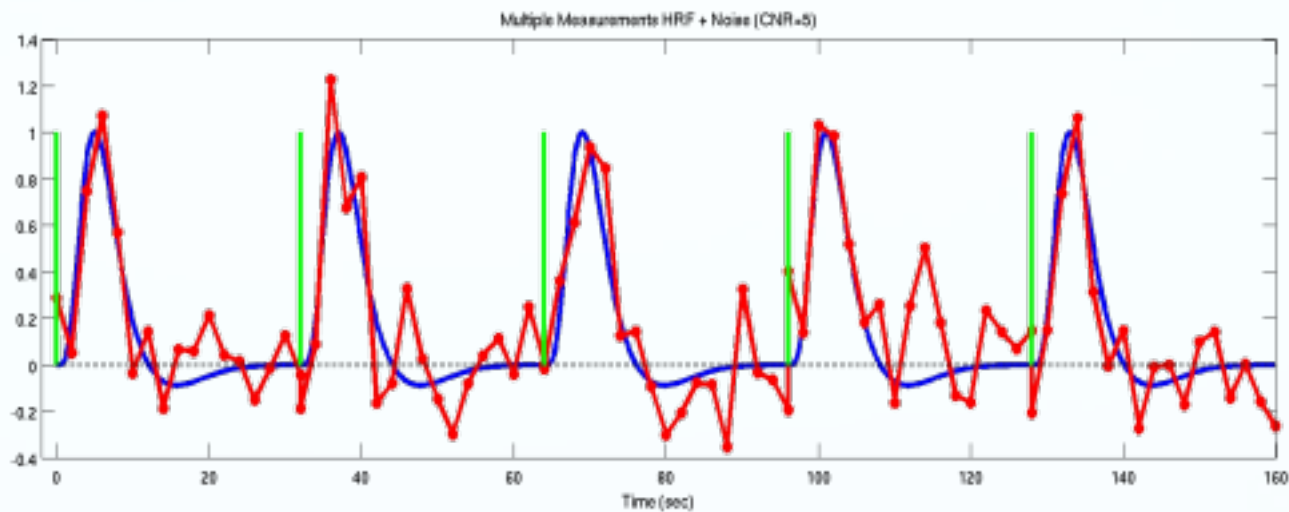
# fMRI Integration

- 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)



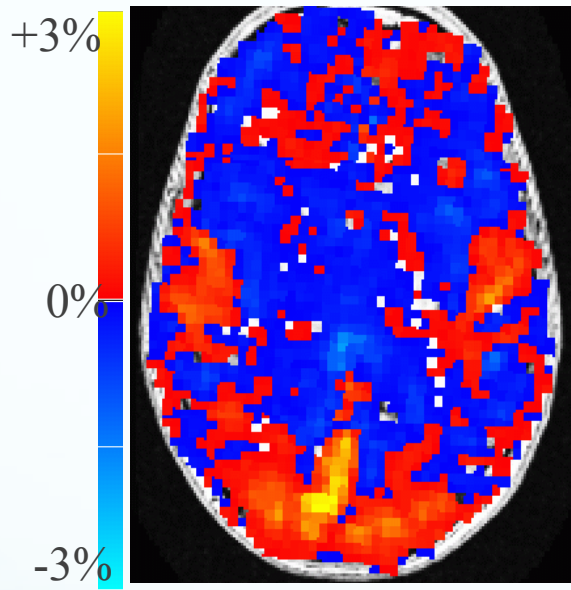
# Multiple Presentations/Averaging



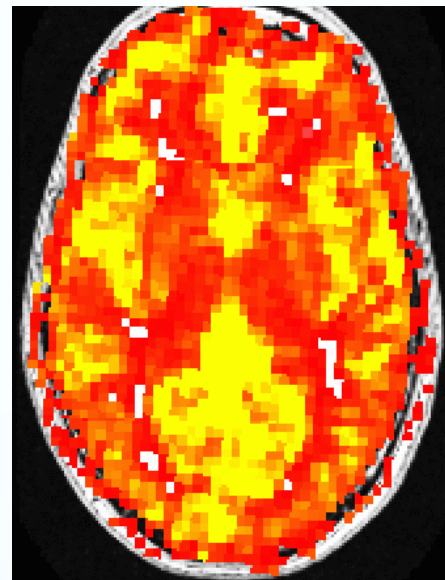
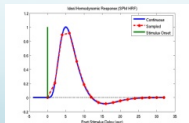
Individual Output: HRF Amp, HRF Var, p/z/t/F



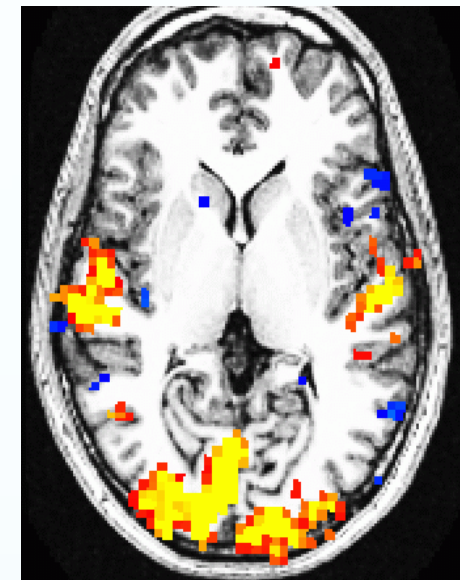
# Statistical Parametric Map (SPM)



Contrast **Amplitude**  
CON, COPE, CES



Contrast Amplitude  
**Variance**  
(Error Bars)  
VARCOPE, CESVAR



**Significance**  
t-Map (p,z,F)  
(Thresholded  $p < .01$ )  
 $\text{sig} = -\log_{10}(p)$

“Massive Univariate Analysis”  
-- Analyze each voxel separately

# fMRI Preprocessing Overview

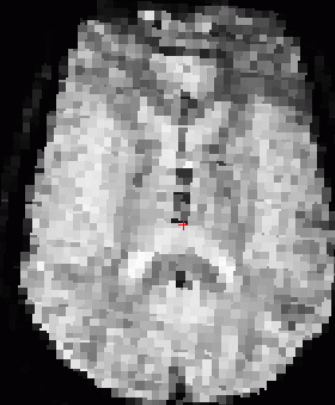
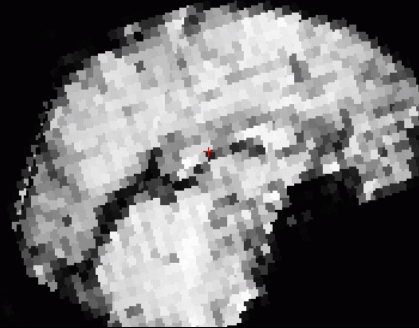
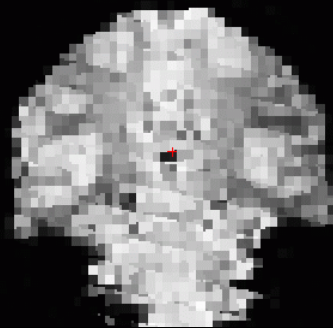
- Motion Correction (MC Template)
- Use reference/template for registration
- `bbregister --mov template.nii --bold --s subject --init-fsl --lta register.lta`
- `freeview -v template.nii:reg=register.lta -f $SUBJECTS_DIR/subject/surf/?h.white`
- Do not use nonlinear resampling to Talairach/MNI space. 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

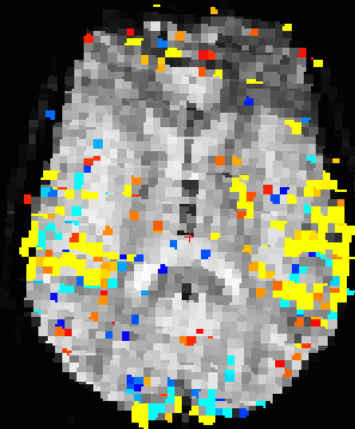
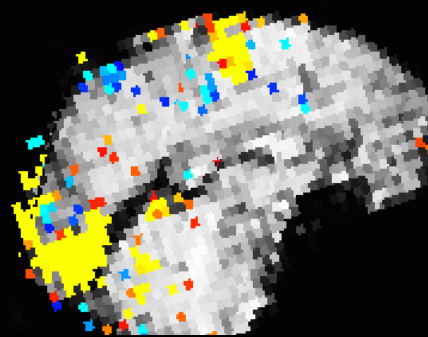
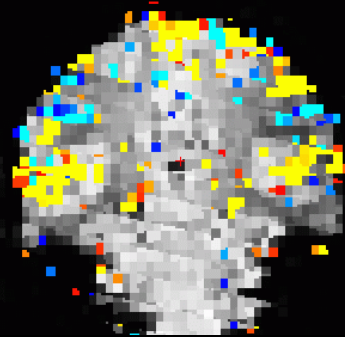
- First-Level (Individual) Analysis
  - HRF Amplitude (or Contrast of Amplitudes)
    - cope (FSL),
    - CON (SPM),
    - ces (FSFAST)
  - Variance of Amplitude
    - varcope (FSL), ??? (SPM), cesvar (FSFAST)
  - Activation/Significance Maps:
    - z, t, F
    - sig ( $-\log_{10}(p)$ )
- All in alignment with MC Template!!!!

# Reference and Map

Functional  
Reference

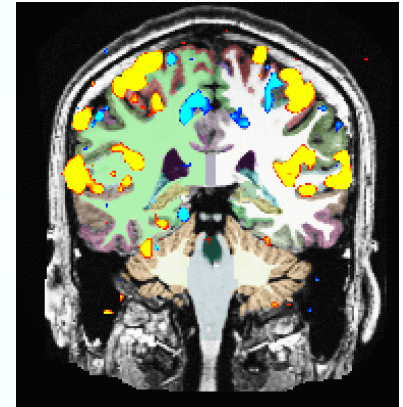


Reference &  
Map



# 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

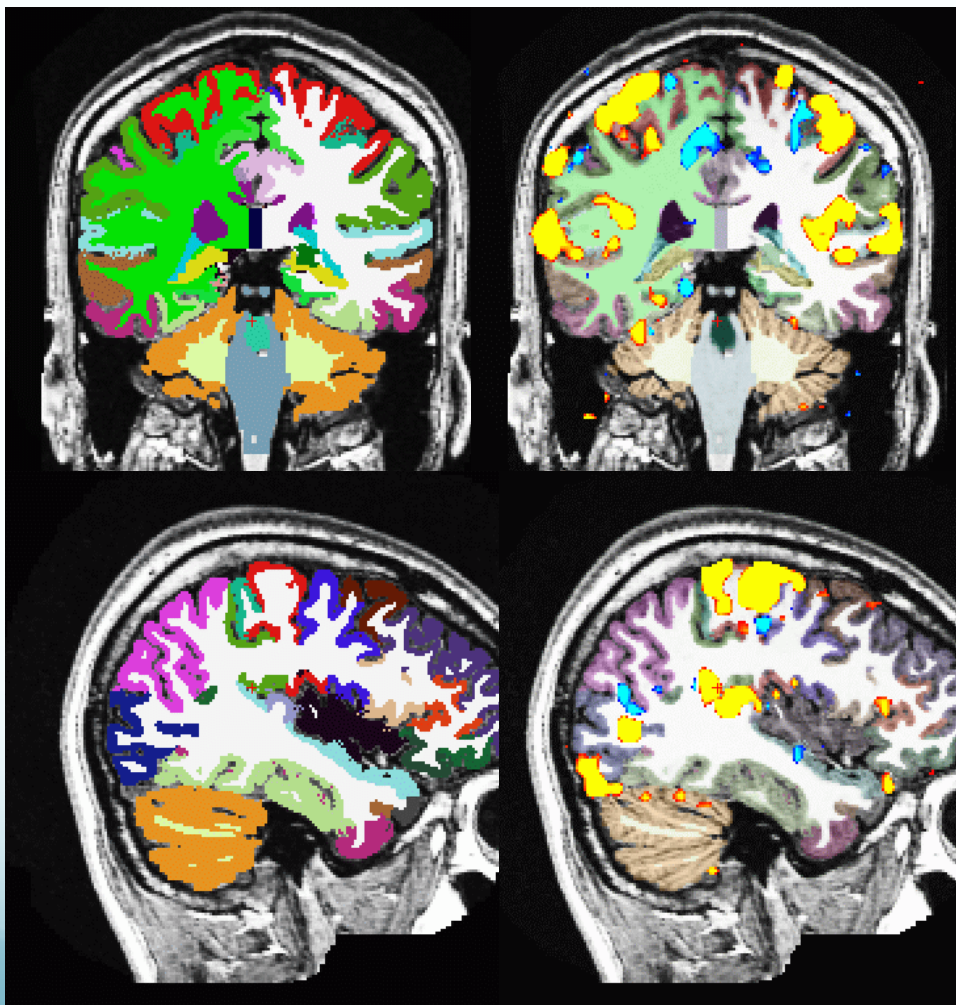
```
freeview -v $SUBJECTS_DIR/fbirn-anat-101.v4/mri/orig.mgz \  
            $SUBJECTS_DIR/fbirn-anat-101.v4/mri/aparc+aseg.mgz:colormap=lut:opacity=.3 \  
            sig.nii:colormap=heat:heatscale=2,3.0,4:reg=register.lta
```

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

**register.lta** – FreeSurfer registration file

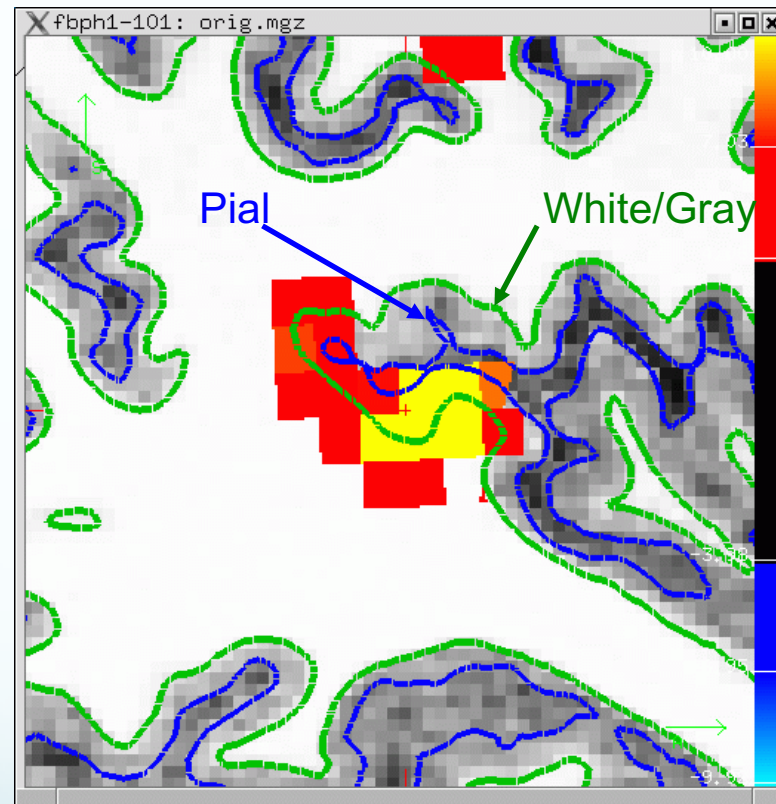
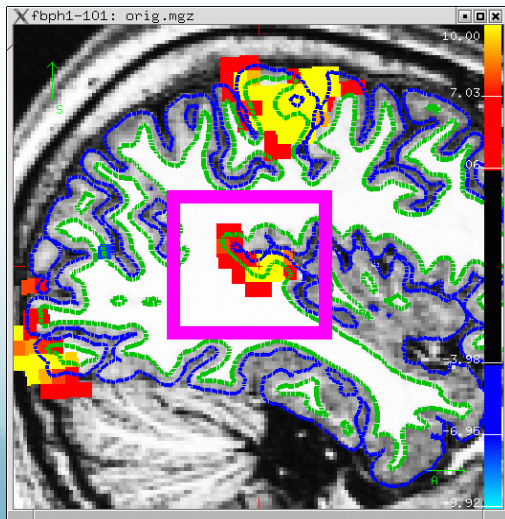
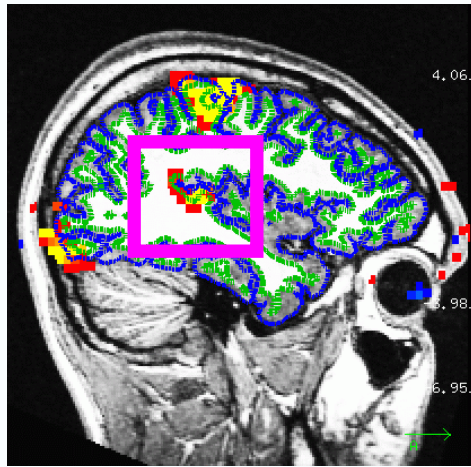
**aparc+aseg** – display aparc+aseg.mgz.  
You can load this from the interface, too.

# Volume Viewing



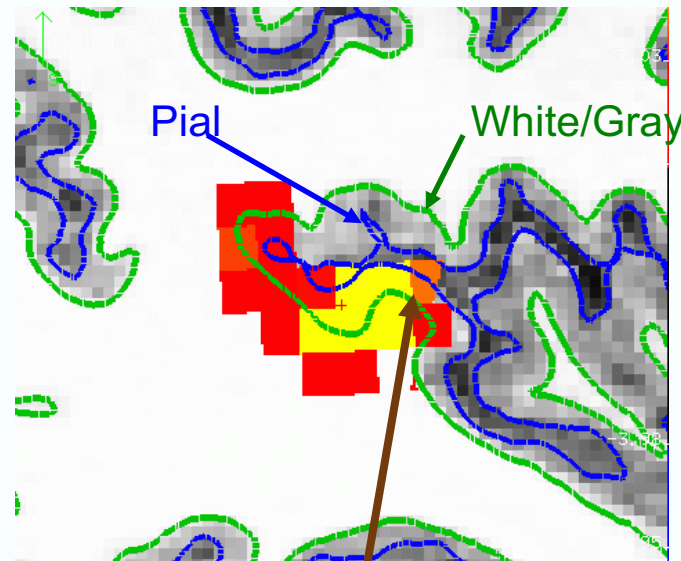
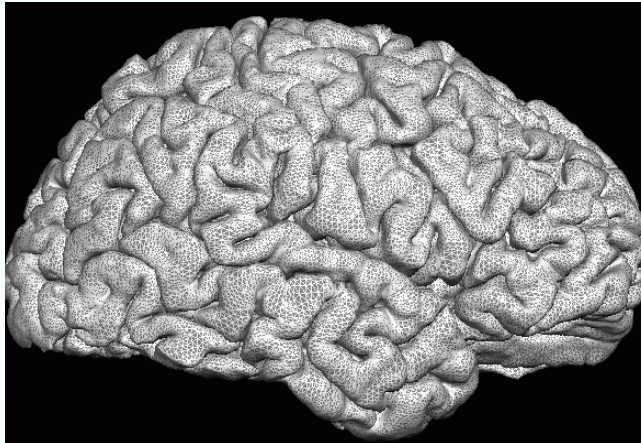
- Red/Yellow +
- Blue/Cyan -
- Seg Opacity
- ROI Average
- ROI Count

# Sampling onto the Surface



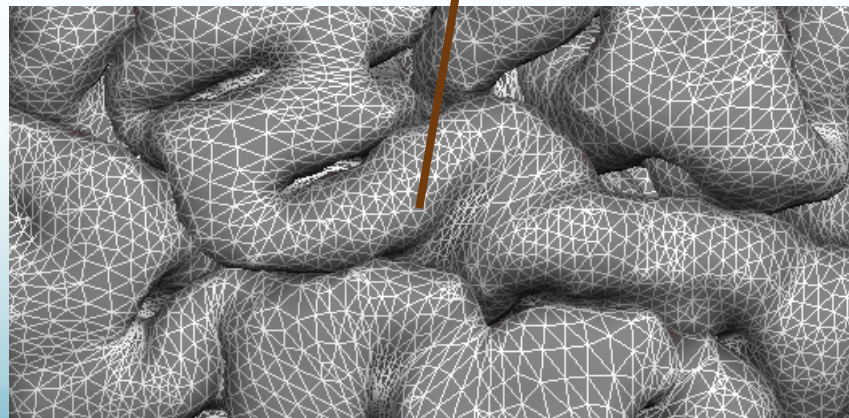


# Sampling onto the Surface

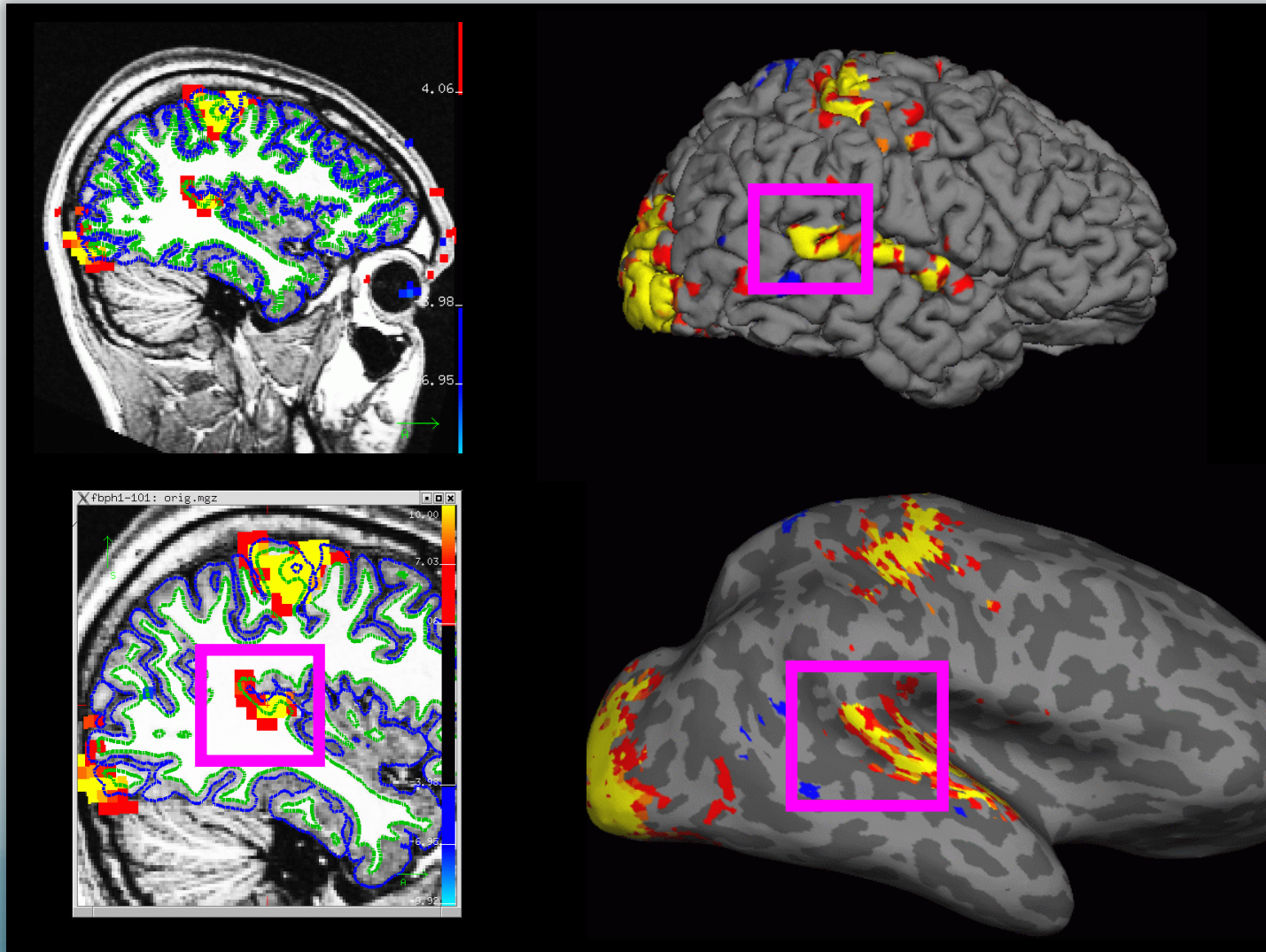


- White/Gray
- Pial
- Half Way
- Average

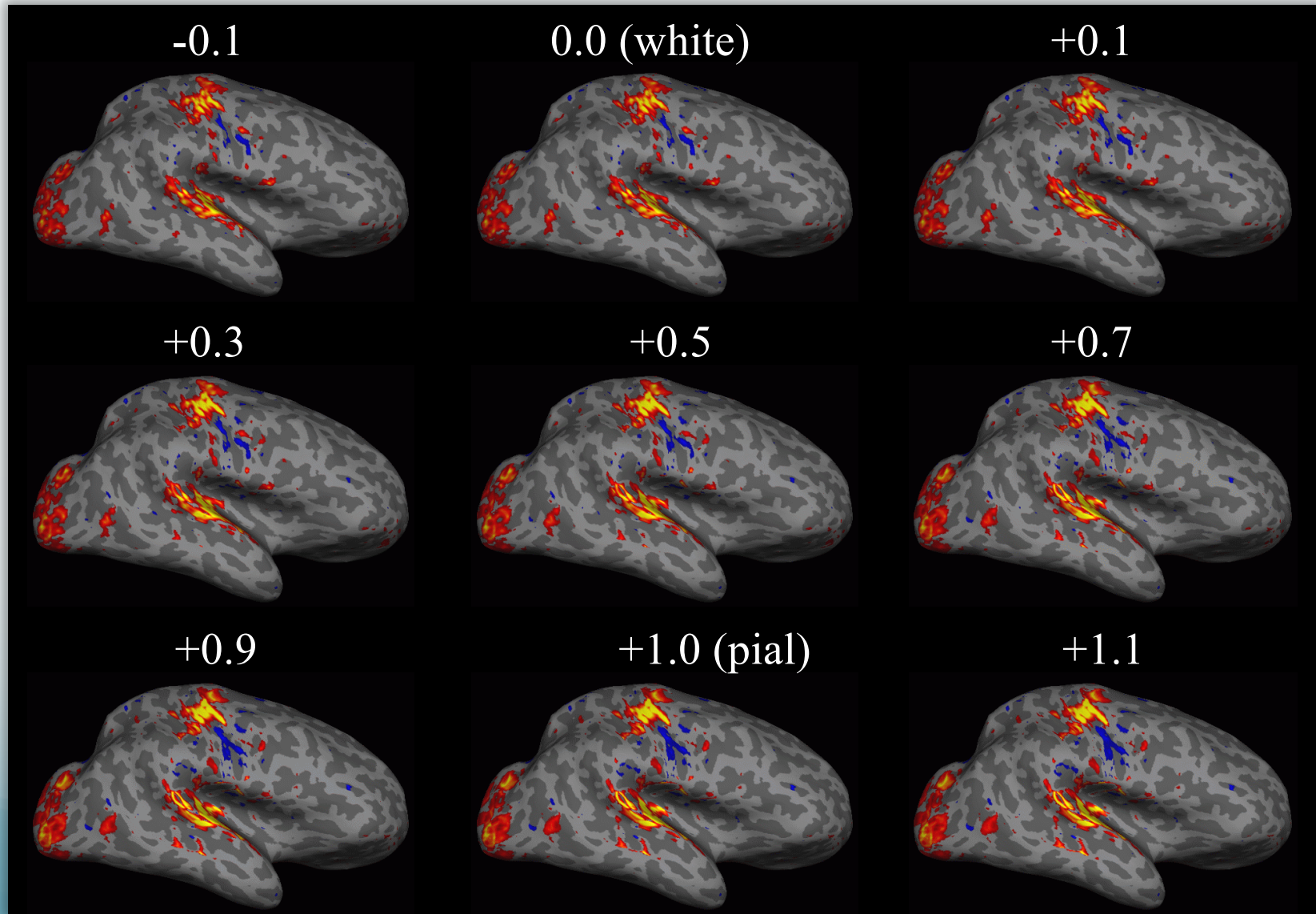
Projection Fraction  
--projfrac 0.5



# Sampling onto the Surface



# Sampling on the Surface: Projection Fraction



# Surface Viewing

## Resample HRF Contrast Significance to left hemisphere

```
mri_vol2surf \  
  --mov sig.nii \  
  --reg register.lta \  
  --hemi lh \  
  --projfrac 0.5 \  
  --o lh.sig.mgh
```

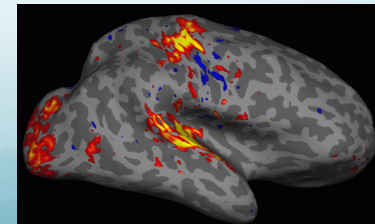
- map in native functional space
- FreeSurfer registration file
- hemisphere
- projection fraction (half)
- output (Nvertices-x-1 mgh format)

Note similarity to `bbregister` command!

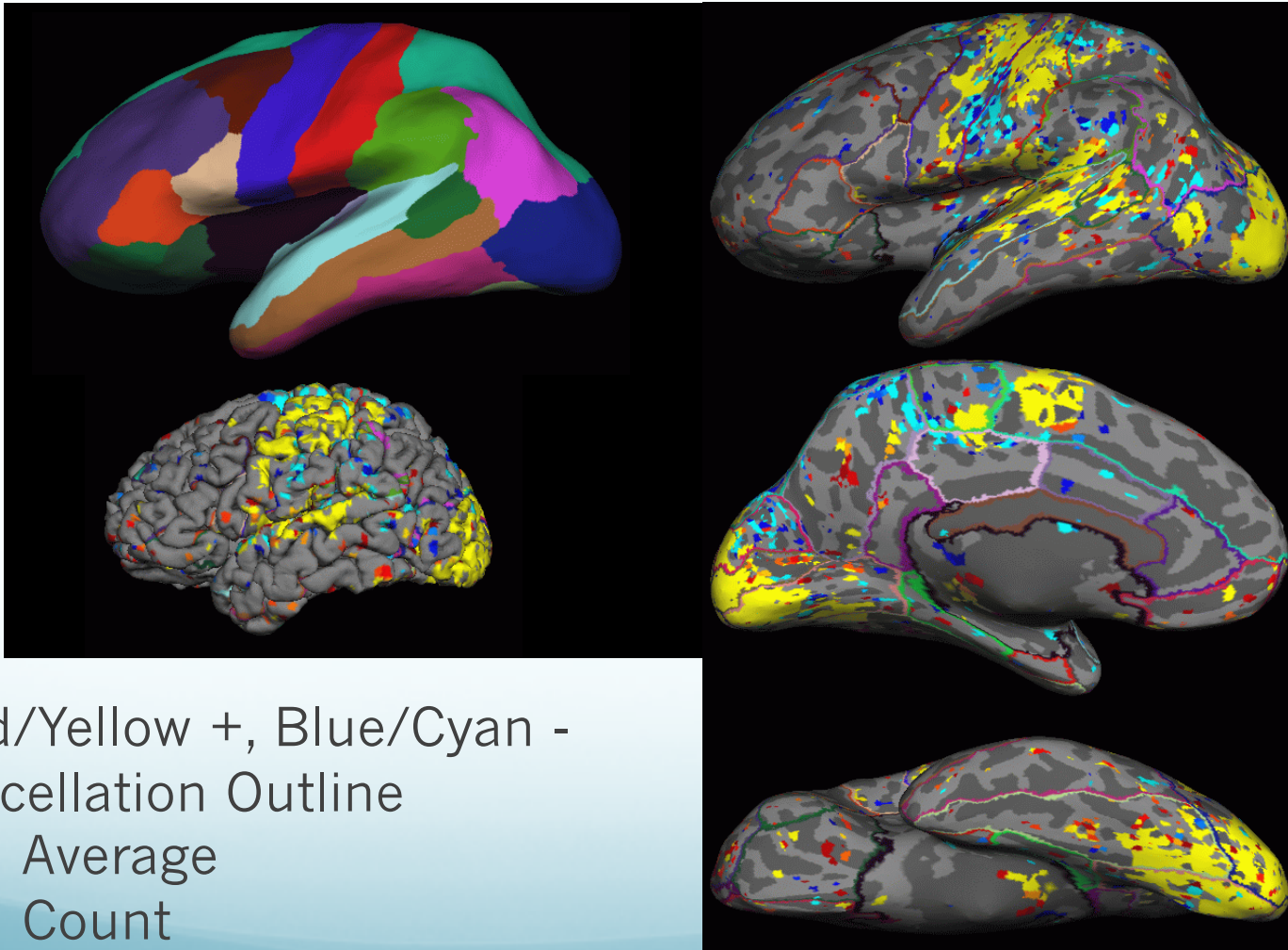
## Load HRF Contrast Significance as overlay

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

```
tkviewer 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
```

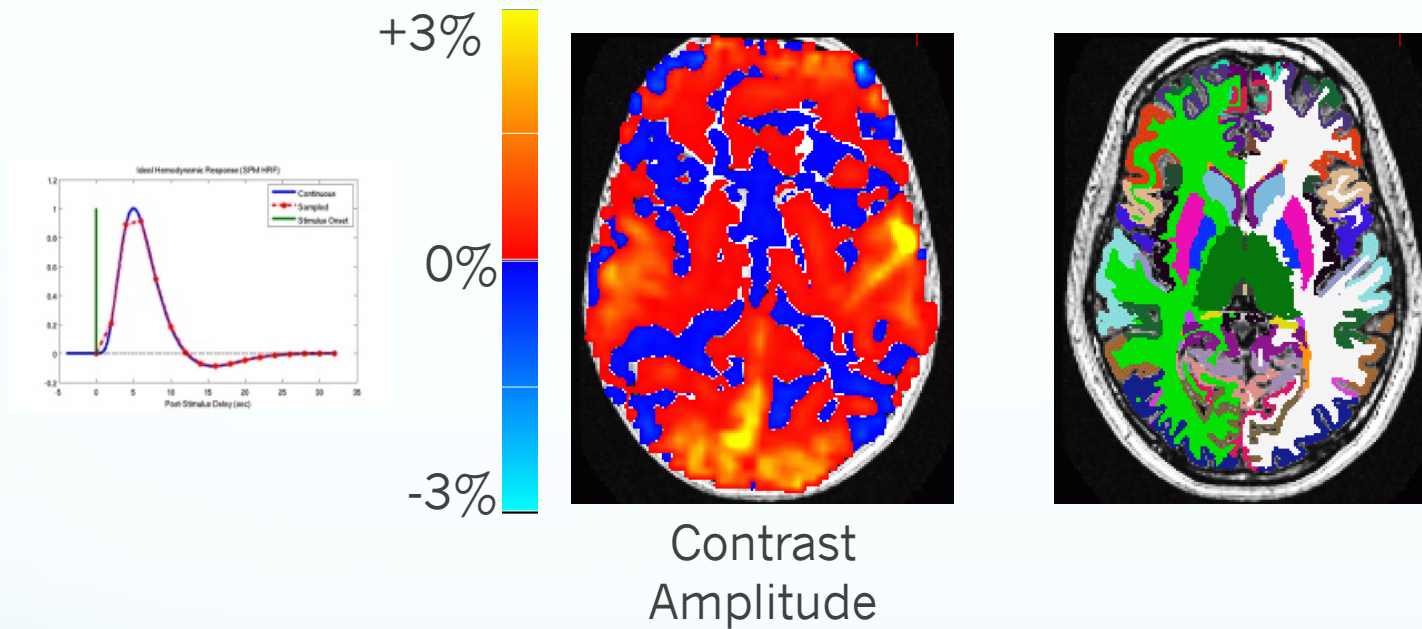
```
mri_glmfit --surf fsaverage lh --cortex \
```

```
--y lh.fsaverage.ces.sm10.mgh ...
```

# fMRI ROI Analysis

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

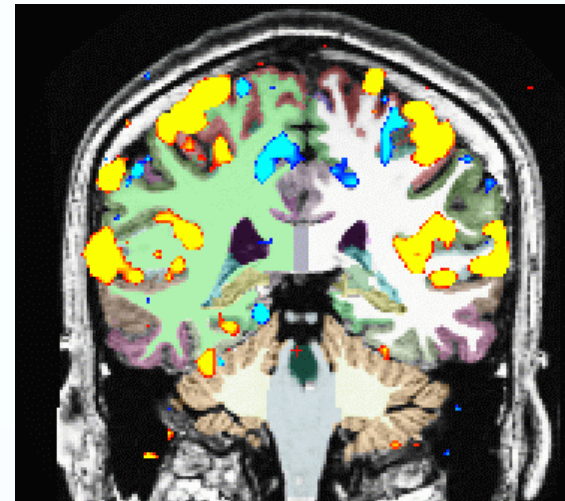
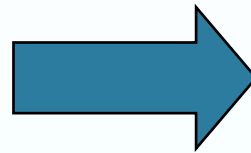
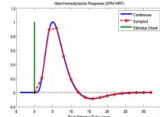
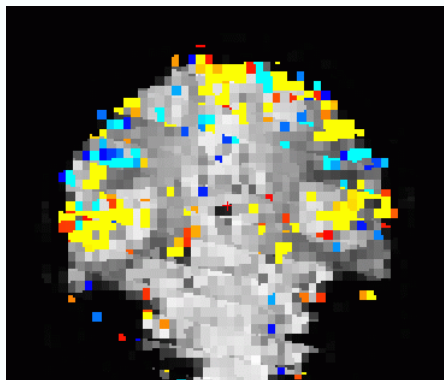
# fMRI ROI Analysis



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

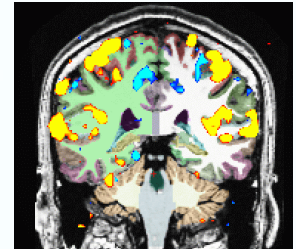
- Command name
- HRF map in functional space
- FreeSurfer Registration File
- Nearest neighbor interpolation
- Specify anatomical output space
- Output file in anatomical space

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
```



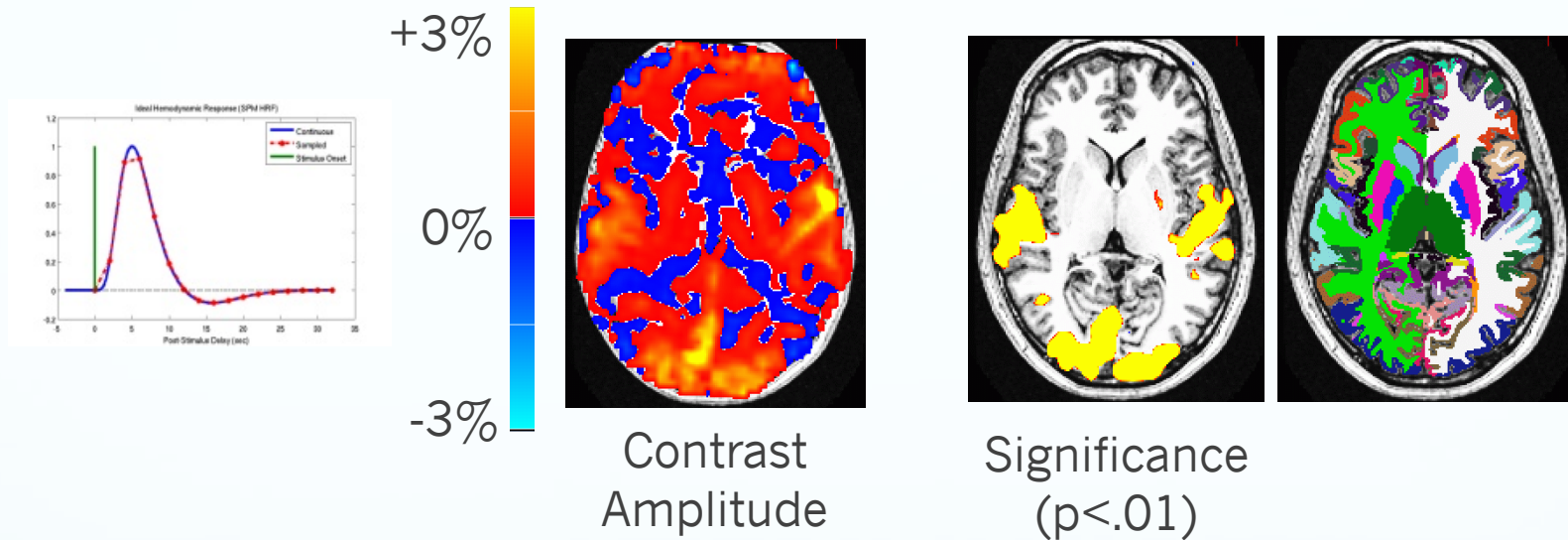
Notes:

- 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.  $p < .01$  ( $\text{sig} > 2$ ) regardless of sign (yellow or blue), or
2.  $p < .01$  ( $\text{sig} > 2$ ) for positive activation (yellow only), or
3.  $p < .01$  ( $\text{sig} > 2$ ) 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 always result in positive HRF average
  - neg will always 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`)