

This is a tool that allows for seed-based connectivity analysis. The tool is inherently batch capable.

Things you will need for using:

- •spm8Batch preprocessed data
- regions-of-interest (either coordinates or images)
- moderate comfort with editing matlab .m files

This tool was developed by Robert Welsh with support from NIH R01NS052514 and released through UM-Psych Methods Core.

To utilize you will need to copy the template code to your working experimental directory and modify to your specific experimental conditions. This template is:

...../MethodsCore/ConnTool/ConnTool\_mc\_batch\_template.m

The following pages will outline the changes you need to implement.

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The basic idea is that you have time-course data and you wish to know the voxel-to-voxel correlations. We interpret consistent correlations as bring a signal of a "connection". Connections can have either positive or negative polarity. These correlations can either be saved as brain-wise correlation images or correlation maps. To use the tool you need to have time-series data for each subject along with some masking images (if you wish to implement physiological correction using COMPCOR like methodology).

Prior to the calculation of the correlations the data are preprocessed.

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Prior to the calculation of the correlations the data are preprocessed.

There are four main sections of the template script

- Input data specification
- Preprocessing specification
- Region of Interest (ROI) specification
- Output specification

#### Input needed:

- •Time series data
- Optional confound time series (same as above but prior to smoothing)
- Optional grey, white, and CSF masks
- Optional brain mask
- Optional files to identify bad temporal frames
- Optional realignment (motion) files

#### **Preprocessing options:**

- Detrending
- •Smooth replacement of spikes (read the literature)
- Motion regression
- •Global signal regression (read the literature)
- White matter regression (via COMPCOR)
- •CSF regression (via COMPCOR)
- Edit spikes by removal (read the literature and see S above)
- •Band-pass filter data

**Bolded** letter is the preprocessing option to be specified.

You may specify any order of preprocessing. However the recommended order is: **DSM[G]CWB[E]** 

August 21, 2013 ConnTool <u>rcwelsh@med.umich.edu</u>

#### Region of interest:

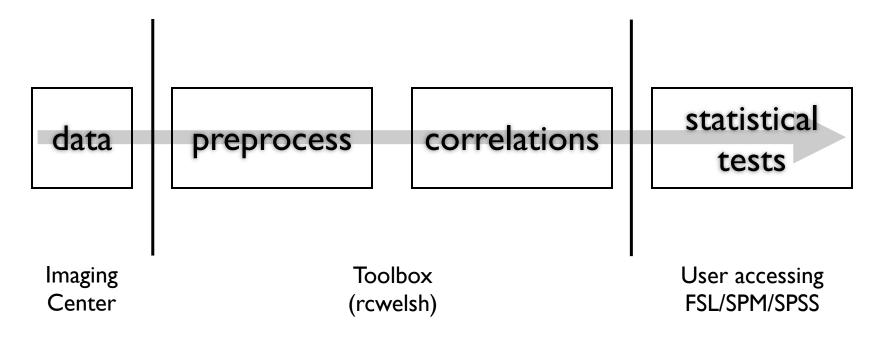
Regions of interest can be specified in multiple ways, including images and specific coordinates.

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#### **Output:**

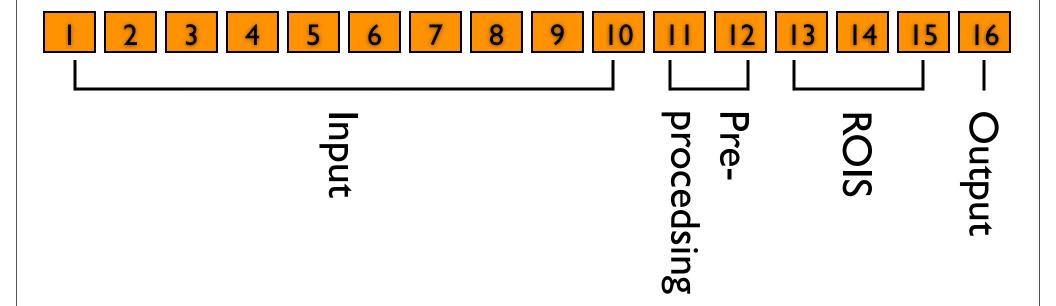
You may specify output as either "images" or "maps". Images are NIFTI 3D images of r-correlation and z's. Maps are saved to a '.mat' file for further calculations.

Domain Responsibility



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Details on things to change in the script to execute a connectivity analysis



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```
%%% GENERAL OPTIONS
%%% These options are shared among many of our scripts
   %%% The folder that contains your Subjects folders
Exp = '/Volumes/ALS/ALS2008/';
%%% The list of subjects to process
%%% The format is 'subjectfolder',[runs to include]
SubjDir = {
   '111129eb',[1];
   '111109ma',[1];
%%% Specify a subject of the above by indicating which rows
%%% of subjects to include in the current job.
%%% One number per subject you want. If you leave this empty all
%%% subjects will be processed.
SubjectDirBatch = [1 2];
    Path where your images are located
응응응
    Variables you can use in your template are:
응응응
                = path to your experiment directory
        iSubject = index for subject
응응응
        Subject = name of subject from SubjDir
                  (using iSubject as index of row)
        iRun
                = index of run (listed in Column 3 of SubjDir)
        Run
                = name of run from RunDir (using iRun as index of row)
응응응
                = wildcard (can only be placed in final part of template)
%%% Examples:
%%% ImageTemplate = '[Exp]/Subjects/[Subject]/func/run 0[iRun]/';
%%% ImageTemplate = '[Exp]/Subjects/[Subject]/TASK/func/[Run]/'
ImageTemplate = '[Exp]/Subjects/[Subject]/connect/func/[Run]/';
%%% A list of run folders where the script can find functional images
RunDir = {
   'run 01';
   };
```



Specify the top-level directory of your experiment.

List of subjects and run numbers to use for each subject.

Option subset to process.

Generic path to your timeseries data.

List of runs for processing.

```
%%% The file to extract the CSF and WM confounds from
응응응
%%% It usually the run file that is in MNI space but prior
%%% to smoothing. The idea is that you don't want gray
%%% smoothed into the CSF or WM regions.
%%% This can be the same file as the 'connectFile', but not ideal.
%%% The code implements COMPCOR based on the paper of:
응응응
%%% Behzadi Y, Restom K, Liau J, Liu TT. A Component Based Noise
%%% Correction Method (CompCor) for BOLD and Perfusion Based fMRI.
%%% NeuroImage 2007;37:90?101.
confoundFile = 'w3mm_vbm8_ra8_run';
%%% The file to run the connectivity on
%%% This will be the smoothed and warped to MNI file.
connectFile = 's5mm w3mm vbm8 ra8 run';
%%% Image Type should be either 'nii' or 'img'
%%% Where possible please use "nii" files types.
%%% NOTE: Eventually img/hdr support will be depricated.
imagetype = 'nii';
```

Name of time-series for confound. It should be your unsmoothed data.

Name of time-series

Image type used

```
%%% The TR your data was collected at
TR = 2;
%%% Number of Functional scans to use per run
%%% (if you have more than 1 run, there should be more than 1 value here)
응응응
%%% e.g. if you have three runs it should be:
응응응
       NumScan = [240 240 240];
응응응
%%% If you have subjects with varying number of time points you can pick
%%% the smallest, that will trim them down so they all have the
%%% same effective statistical power.
응응응
응응응
%%% If you are unsure you may enter a super big number and all points
%%% will be taken.
NumScan = [9999 9999];
```

Sample period of your timeseries data.

How many time-points to use for each run.

```
4
```

```
CONNECTIVITY OPTIONS
%%% These options are only used for Connectivity
%%% Mode to run ConnTool batch mc central in
응응응
       'test'
                    = test script but do not save parameters or run any
응응응
                       ConnTool code
응응응
       'parameters' = run script and save parameters for each subject
                          but do not run any ConnTool code
응응응
응응응
       'presave'
                    = run ConnTool code on previously saved parameters
응응응
       'full'
                    = generate parameters and immediately run ConnTool code
      NOTE: If you choose mode 'presave' then most variables except
응응응
          SubjDir and OutputTemplate/OutputName will be ignored as they
          will be loaded from the already existing parameter file for each
          subject.
응응응
Mode = 'full';
```

Mode to run in, if you're unsure just specify 'full';

```
Pointers to for anatomic images.
응응응
       AnatomyMaskPath --- this should point to the VBM8 processed data
응응응
응응응
       GreyFile --- name of a grey matter image from VBM8.
응응응
                      Just leave blank, in general don't use this option.
응응응
응응응
       WhiteFile --- name of the WM image produced by VBM8
                      Typically this starts with "WM ero"
응응응
       CSFFile --- name of the CSV image produced by VBM8
응응응
                      Typically this starts with "CSF ero"
%%% NOTE: Wildcard "*" can be used in the definition of the file names.
   The white matter and CSF masks are use for COMPCOR
%%% If the grey is specified then a new mask is created which is the AND
%%% of the EPI and the grey. This new mask is used to constrain the
%%% calculations. If you do use this option then you will have a subject
%%% specific mask. This may make doing group analysis troublesome if you
%%% are using 'maps' as the output.
AnatomyMaskPath = '[Exp]/Subjects/[Subject]/connect/func/coRegRARUN/VBM8/';
GreyFile = 'w3mm vbm8 p1ht1spgr.nii';
WhiteFile = 'WM ero*.nii';
CSFFile = 'CSF ero*.nii';
%%% Path and name of explicit mask to use at subject level.
%%% Leaving this blank ('') will use a subject-specific mask
응응응
%%% The EPI mask is used to calculate only in brain.
%%% NOTE: Subject-specific masks are NOT recommended at all.
EPIBrainMaskTemplate = ...
    '[mcRoot]/ConnTool/Templates/symmetric 3mm EPI MASK NOEYES.nii';
```

Information on where to find the output of the vbm8HiRes command.

Path and name of your brain mask. If you are using 3mm voxels the default should work for you.

```
6
```

You can safely leave these alone.

Where to find the realignment files (output from realignfMRI)

```
%%% Path Template for pre-filter replacement of spikes.
응응응
%%% This file does NOT have to be present for each subject. If the file
%%% is missing then it's assumed that the correction is not to be done.
응응응
%%% This file should either be a simple text file containing a column-wise
%%% vector of 1s and 0s, or a saved MATLAB .mat file with a
%%% cv variable containing a column of 1s and 0s
응응응
응응응
        'moving#'
                     - local timecourse mean
응응응
                       where # is a real number indicating the window
응응응
응응응
                           DespikeReplacementOption='moving7';
응응응
        'loess#'
                     - robust loess regression smoothing interpolation
응응응
                       where # is a real number indicating the window
응응응
                       e.g.
응응응
                           DespikeReplacementOption='loess0.15';
응응응
        'rloess#'
                     - robust loess regression smoothing interpolation
응응응
                       where # is a real number indicating the window
응응응
응응응
                           DespikeReplacementOption='rloess0.15';
응응응
        'sgolay#'
                     - robust loess regression smoothing interpolation
응응응
                       where # is a real number indicating the window
응응응
                       e.g.
응응응
                           DespikeReplacementOption='sgolay7';
응응응
        'lowess#'
                     - robust loess regression smoothing interpolation
응응응
                       where # is a real number indicating the window
응응응
                       e.g.
응응응
                           DespikeReplacementOption='lowess.15';
응응응
        'rlowess#'
                     - robust loess regression smoothing interpolation
응응응
                       where # is a real number indicating the window
응응응
                       e.g.
응응응
                           DespikeReplacementOption='rlowess0.15';
응응응
응응응
```

```
%%% After the data are smoothed, the missing point is then calculated with
%%% an interpolation(interp1) using pchip (cubic).
%%% This is following:
응응응
       Satterthwaite TD, Elliott MA, Gerraty RT, Ruparel K, Loughead J,
       Calkins ME, Eickhoff SB, Hakonarson H, Gur RC, Gur RE, Wolf DH.
       An Improved Framework for Confound Regression and Filtering for
응응응
응응응
       Control of Motion Artifact in the Preprocessing of Resting-State
응응응
       Functional Connectivity Data.
       NeuroImage 2013;64:240?256.
DespikeParametersTemplate = ...
    '[Exp]/Subjects/[Subject]/connect/func/[Run]/prefilter despike.dat';
DespikeReplacementOption = 'sgolay7';
DespikeReplacementInterp = 'pchip';
```

Despiking information. It is recommended that you despike **prior** to doing bandpass filtering.

```
%%% Path Template for post-filter censoring of spikes.
응응응
%%% This file does NOT have to be present for each subject. If the file
%%% is missing then it's assumed that the correction is not to be done.
응응응
%%% This file should either be a simple text file containing a column of
%%% 1s and 0s, or a saved MATLAB .mat file with a cv variable containing a
%%% column of 1s and 0s
응응응
응응응
        This ConnTool Toolbox users an FFT filter with a little
        bit of smoothing. If you want to censor your data your should
응응응
응응응
        see the following papers.
응응응
응응응
        See the following papers:
응응응
응응응
        Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE.
응응응
        Spurious but Systematic Correlations in Functional Connectivity
응응응
        MRI Networks Arise From Subject Motion. NeuroImage 2012
응응응
응응응
        Carp J. Optimizing the Order of Operations for Movement Scrubbing:
응응응
        Comment on Power Et Al. NeuroImage 2012
응응응
응응응
        Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE.
응응응
        Steps Toward Optimizing Motion Artifact Removal in Functional
응응응
        Connectivity MRI; a Reply to Carp. NeuroImage 2012.
응응응
응응응
        Satterthwaite TD, Elliott MA, Gerraty RT, Ruparel K, Loughead J,
응응응
        Calkins ME, Eickhoff SB, Hakonarson H, Gur RC, Gur RE, Wolf DH.
응응응
        An Improved Framework for Confound Regression and Filtering for
응응응
        Control of Motion Artifact in the Preprocessing of Resting-State
응응응
        Functional Connectivity Data.
응응응
        NeuroImage 2013
응응응
응응응
       Fair, D. et al. Distinct Neural Signatures Detected for ADHD
응응응
        Subtypes After Controlling for Micro-Movements in Resting State
응응응
        Functional Connectivity MRI Data. Front in Sys Neuro 2013
```

Scrubbing information. If you choose to scrub post filtering you should understand the mathematical concept of Gibbs ringing.

Also see the document:

Spike-Filtering-Interaction.pdf in the Documentation folder.

```
П
```

```
응응응
%%% DETREND Polynomial order
응응응
응응응
      A number, 0-mean
응응응
                 2-quadratic, starting to get the idea?
DetrendOrder = 2;
   The code users COMPCOR.
%%% Use this many principle components for regression
%%% for the CSF and WM
888
%%% PCA COMPCOR Parameter
          Fraction - fraction of variance for principle components
응응응
%%% Behzadi Y, Restom K, Liau J, Liu TT.
%%% A Component Based Noise Correction Method (CompCor) for BOLD and
%%% Perfusion Based fMRI. NeuroImage 2007;37:90â€"101.
PrincipalComponents = 5;
Fraction
%%% Bandpass Filter Settings
응응응
           LowFrequency - low frequency cutoff
응응응
           HighFrequency - high frequency cutoff
           Gentle - 0 = no rolling, 1 = rolling, 2 = extra rolling
           Padding - number of timepoints to pad on beginning/end
           BandpassFilter - 0 = Matlab filter, 1 = SOM Filter FFT
LowFrequency = 0.01;
HighFrequency = 0.1;
Gentle
               = 1;
Padding
               = 10;
BandpassFilter = 1;
```

Detrending polynomial order

How many components to use from the PCA and what fraction of the data (based on variance ranking) to use.

Band-pass filtering information and "Fraction" is for the PCA analysis. In general you can use these defaults.

```
the order to perform the regressions etc
            D = detrend
                             - Nth order detrend
            S = despike
                             - by replacement
           M = motion
                            - by regression, includes dM/dt
응응응
           G = global
                             - Controversial, you should know the lit.
           W = white matter - by PCA
           C = csf
                             - by PCA
            B = bandpass
                             - by method selected.
           E = edit
                             - by removal
            Suggested order is "DSM[G]CWB"
RegressOrder = 'DMCWEB';
%%% You can save the time course of a single voxel at each step of the
%%% processing to get a sense of what happens.
%%% Leave empty if you don't want it.
응응응
%%% If you do choose to save a voxel time series it will be in the
%%% 'parameters' structure under 'parameters.data.run.sampleTC
%%% each row of the sampleTC is a time-course of the data. The raw time
%%% course will be the 1st row. If detrending is the first RegressOrder
%%% option then the 2nd row will be the data after it's been detrended and
%%% so forth.
voxelIDX
               = 1;
```

The order of doing the preprocessing

Sample voxel to save for plotting

```
13
```

```
%%% Type of input
            coordinates - provide the center of each seed and a radius
            coordload
                      - load corridnate from the specified file
응응응
            files
                        - provide a list of ROI files
                       - provide a directory containing ROI files and the
응응응
                          script will load all images in that directory to
                          use as ROIs
응응응
            grid
                        - make a grid based on provided spacing and masked
                          by provided mask
            gridplus
                        - make a grid based on provided spacing and masked
                          by provided mask, as above. Additionally, add
                          the extra ROI points specified in ROIGridCenters
ROIInput = 'coordinates';
```

What method to specify coordinates for seeds.

```
%%% 'coordinates' method
응응응
   If specifying ROI coordinates you need to provide a list of centers in
%%% MNI coordinates (mm) and a radius in voxels.
%%% NOTE: ROISize will be used as the radius (in voxels, can be fracional
%%% of a sphere at each point.
%%% If you'd prefer to use the predefined 1,7,19, or 27 voxel
%%% sizes you will need to specify the size as a cell (i.e. {19})
%%% See the MethodsCore/ConnTool/Documentation for more help on ROI size.
%%% You can load a file into the array ROICenters.
응응응
%%% If a ".csv" file you would do:
응응응
      ROICenters = load('myROIs.csv');
ROICenters = [0 - 48 \ 26];
          = \{19\};
ROISize
%%% 'coordload' method
%%% If a '.mat" file you need make sure it contains a single array
%%% with each row being an ROI and columns are x,y,z, in MNI mm.
ROIFile = '[mcRoot]/ConnTool/Templates/V MNI 12mmgrid.mat';
ROISize = \{19\};
```

Explicitly list your ROIs in the array, one per row. And specify how many voxels in each ROI. See the ROI information at the end of this document.

The code can read in a CSV files of coordinates (one row per x-y-z, or it can read a matfile and assuming a single array will use that array to assign the ROIs.

```
15
```

Specify a directory to read all images from ('directory') or to read the list of files ('files') from.

The code can place a grid of ROIs on the brain. You specify the spacing in mm and how big to make each ROI. You also need to specify a brain mask.

Extra ROIS to add to the list if you wish.

```
%%% 'files' and 'directory' methods
응응응
%%% If specifying ROI images you need to provide an ROI folder as well as a
%%% cell array list of ROI images. If specifying an ROI directory, you
%%% only need to specify an ROITemplate. The script will then load all
%%% images in that directory to use as the ROIImages cell array.
ROITemplate = '[Exp]/ROIS';
ROIImages = {
    'image1.nii';
    'image2.nii';
    };
응응응
%%% 'grid' and 'gridplus' methods
%%% If specifying ROI grid you need to provide a spacing and ROI size as
%%% well as an optional mask for grid point inclusion (a mask is strongly
%%% encouraged as not using one will return coordinates from across the
%%% entire bounding box).
%%% NOTE: ROIGridSize will be used as the radius of a sphere at each grid
%%% point. If you'd prefer to use the predefined 1,7,19, or 27 voxel sizes
%%% you will need to specify the size as a cell (i.e. {19})
ROIGridSpacing
                    = 12;
ROIGridSize
                    = \{19\};
ROIGridMaskTemplate = ...
    '[mcRoot]/ConnTool/Templates/symmetric_3mm_EPI_MASK NOEYES.nii';
%%% 'gridplus' extra
%%% ROIGridCenters is used in 'gridplus' mode to specify additional ROIs
%%% that you would like to include in addition to the regular grid. They
   will be added to the end of the list of ROIs and will use ROIGridSize
%%% for sizing.
ROIGridCenters = [
    10 10 10;
    -10 10 10;
    -22 \quad 0 \quad -22;
    22 0 -22;
    1;
```

```
%%% Where to output the data and what to call it.
OutputTemplate = '[Exp]/FirstLevel/[Subject]/[OutputName]/';
OutputName
               = 'ConnToolTest5';
%%% Type of output
응응응
         images - output R and Z images of correlation with each seed
응응응
         maps - output R,P, and Z matrices of correlations between seeds
OutputType
              = 'images';
%%% Options for 'maps'
응응응
         correlation type can be 'full' or 'partial'
         You can also save the power spectrum of the ROIS when running
         in 'maps' mode. This will only save the power spectrum of
         single run.
응응응
            1 - save power spectrum
응응응
            0 - do not save power spectrum
         save ROI time courses
            1 - save ROI time courses to same location as R and P matrices
            0 - do not save ROI time courses
     OutputCorrType = 'full';
OutputPower
              = 0;
saveroiTC
              = 0;
```

Name of output

Do you want correlation matrices or images.

If running "maps" and your number of ROIS<<timePoints then you can run 'partial' correlation instead of 'full' You can also save the power-spectrum of ROIs and the time-courses as well.

Once you have the code edited appropriately you can execute from the matlab command line. I suggest that one you run the command to then archive as a record for later use.

For each subject a log file, a parameters file, and the results file are created. These will be in the FirstLevel directory tree you specified. If your option was for image output you can treat those as "contrast" images and enter them into a second-level analysis. You should take the **zmap** images.

Supplementary Information

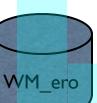
## Input

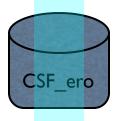
## Connectivity Toolbox Output How-To (a sketch)

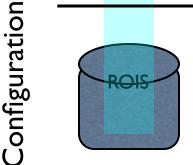
# time-series data

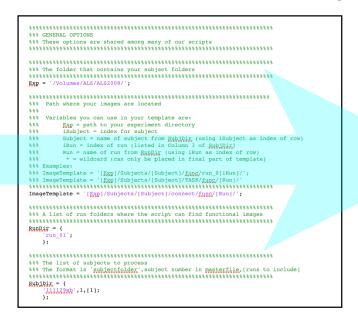
#### ConnTool\_mc\_batch\_template

realign.dat





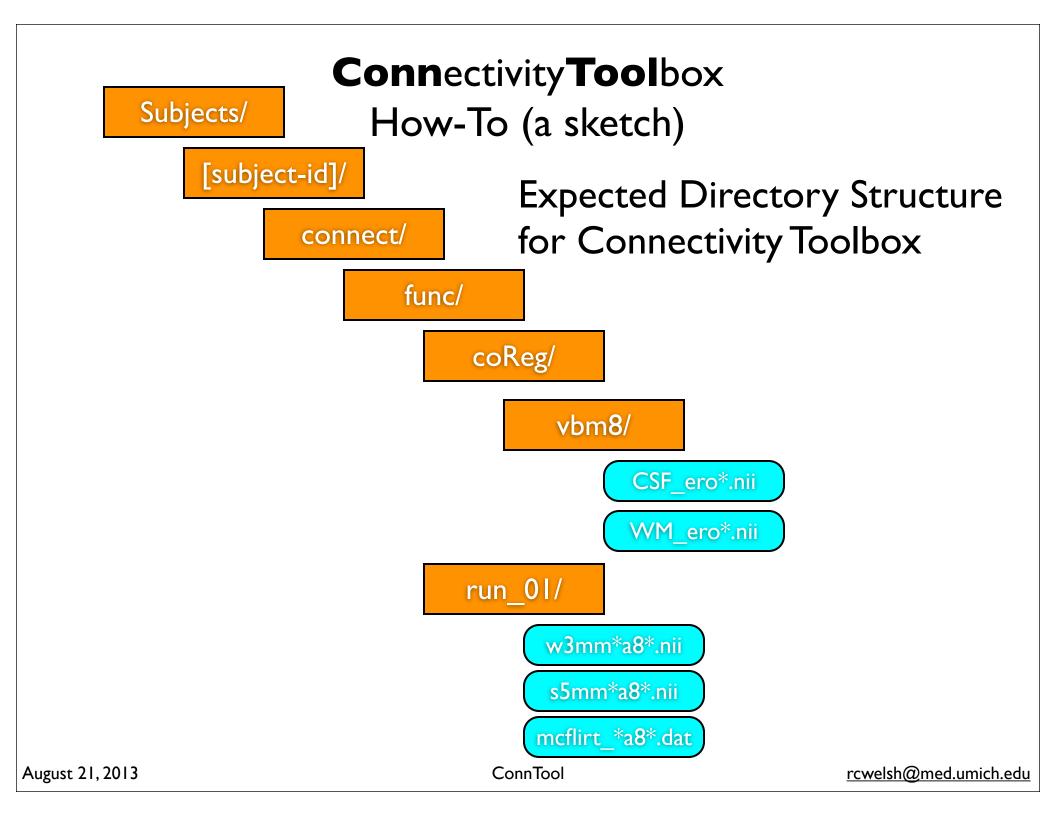


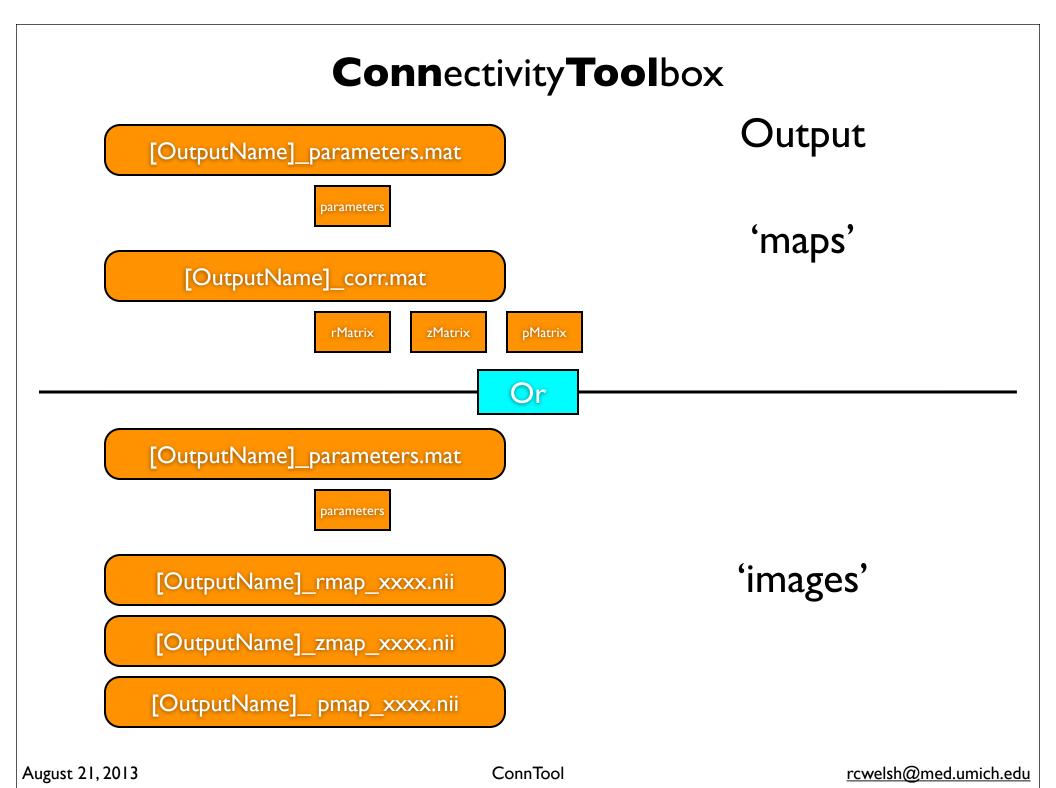




With the script you specify input data, and control parameters for how the analysis will proceed, which in turn will produce output matrices or images.

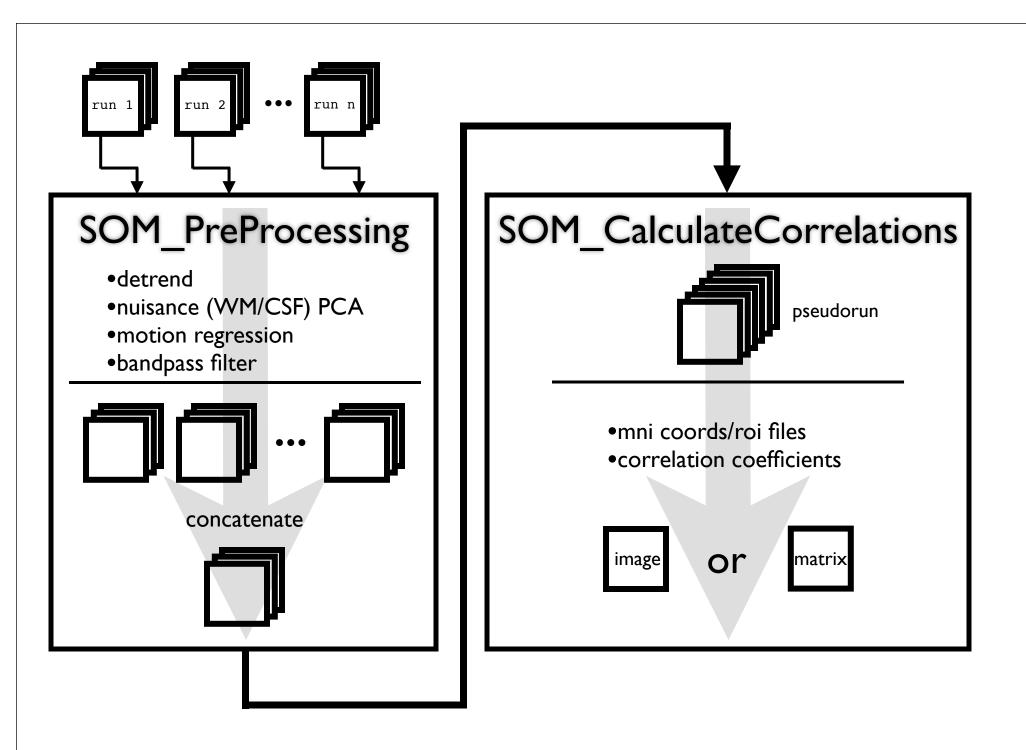
Subject data

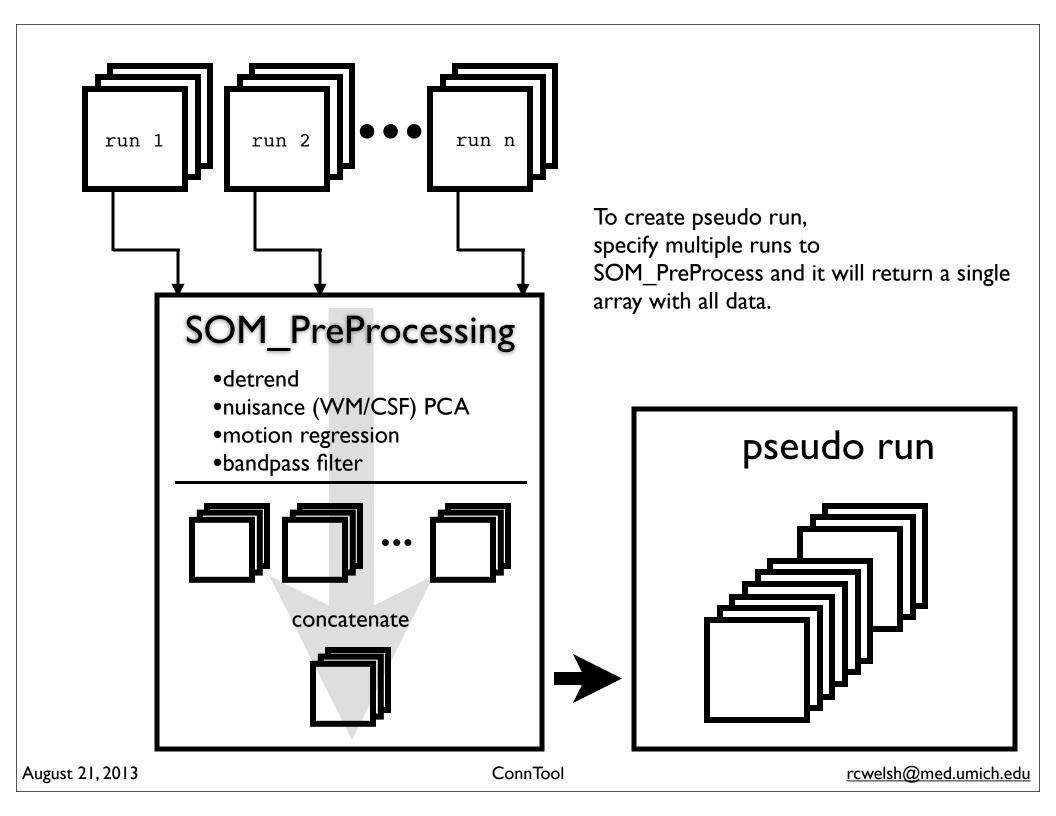




If you like you may concatenate runs into a single connectivity run. The concatenation takes place after the preprocessing.

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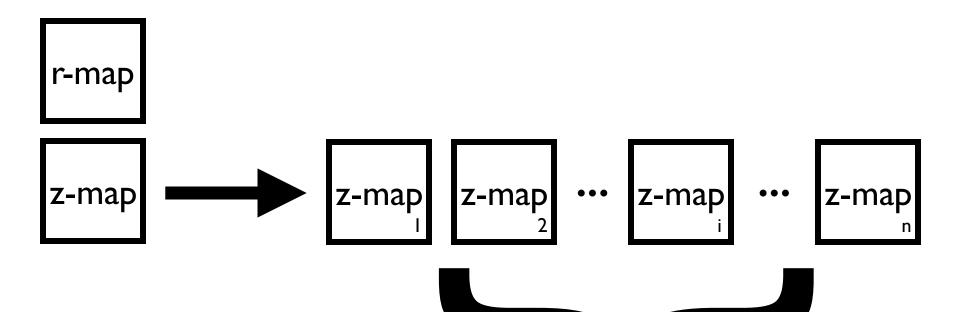


# Connectivity Toolbox How-To (a sketch)

Output can be either the 'maps' or 'images'. Images can be used in SPM just as you would a contrast images. Maps are written to a MATLAB .mat file in the output directory. To use those you will need to be familiar with matlab matrices.

# Now what?

#### Image based



Treat the z-maps just like you would contrast maps and take to second level.

t-test I or 2-sample etc.

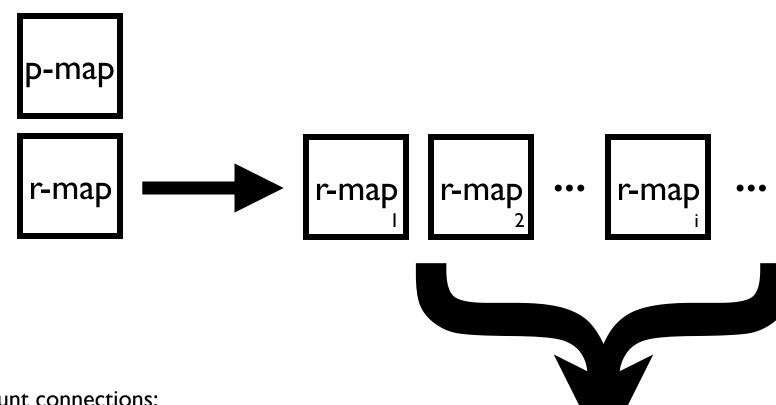
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ConnTool

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#### mat based

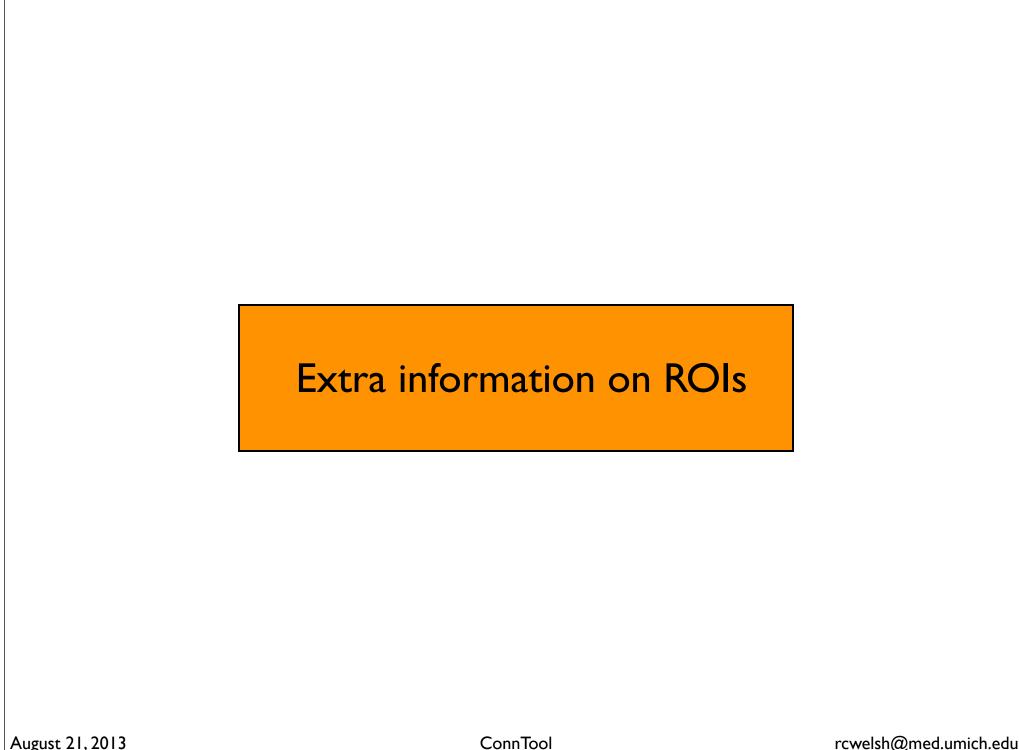
# Now what?



Count connections:

e.g. count connections between nodes that pass a given p-threshold. this can be done on the single subject level etc.

perform whatever statistic fits your fancy. do on r-maps or on p-maps.



### **Defining ROIs**

You can use the built-in ROI standard objects, or you can specify you own. Recognized sizes are 1, 7, 19, 27.

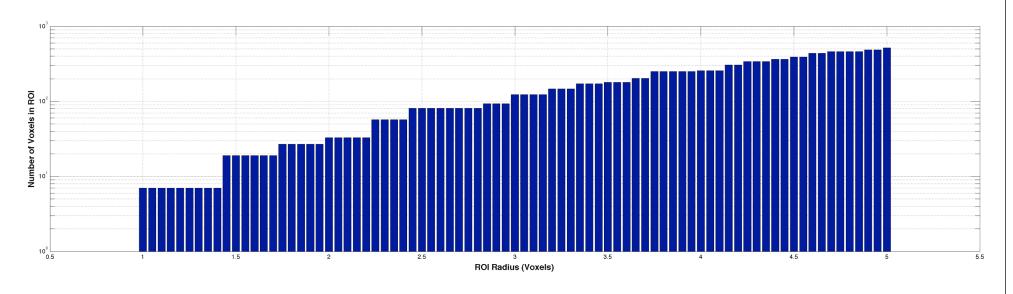
```
parameters.mni.
  coodinates = [x_0 \ y_0 \ z_0;
                        x_1 y_1 z_1;
                        x_n y_n z_n;
   size
                     = #;
   size.XROI
                     = [-1 \ 0 \ -1];
                     = [ 0 0 0 0 ];
        .YROI
        .ZROI
                     = [0 0 0 0];
```

#### So specify you own use:

#### Or, have the code build the arrays

```
XYZ = SOM_MakeSphereROI(radius);
parameters.rois.mni.size.XROI=XYZ(1,:);
parameters.rois.mni.size.YROI=XYZ(2,:);
parameters.rois.mni.size.ZROI=XYZ(3,:);
```

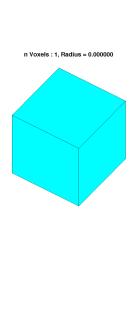
Obviously, some range of radii will give same ROI definition.

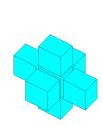


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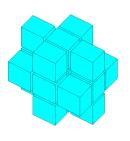
ConnTool

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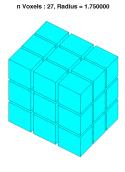




n Voxels : 7, Radius = 1.000000



n Voxels : 19, Radius = 1.450000



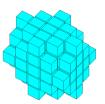
n Voxels : 33, Radius = 2.000000



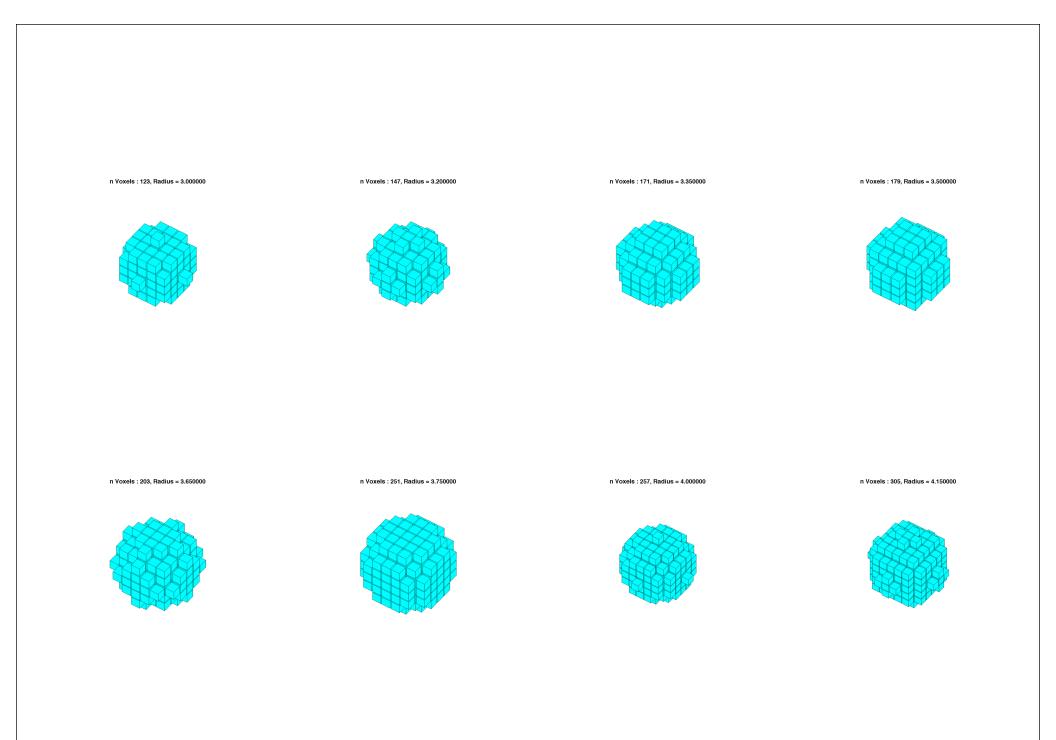
n Voxels : 57, Radius = 2.250000

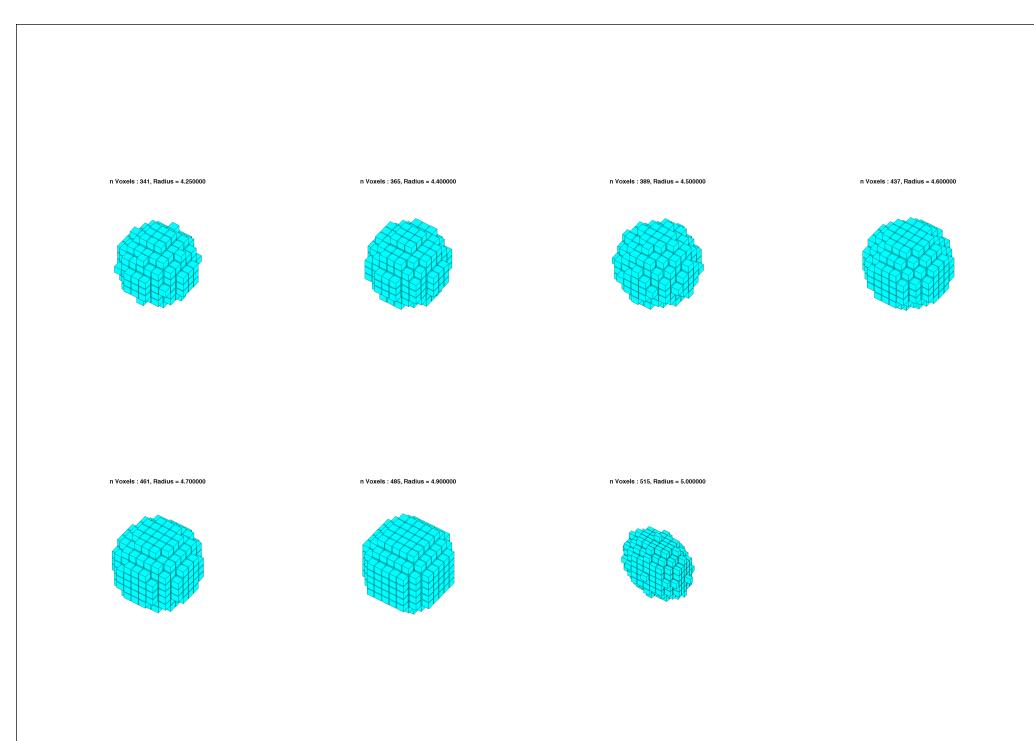
n Voxels : 81, Radius = 2.450000



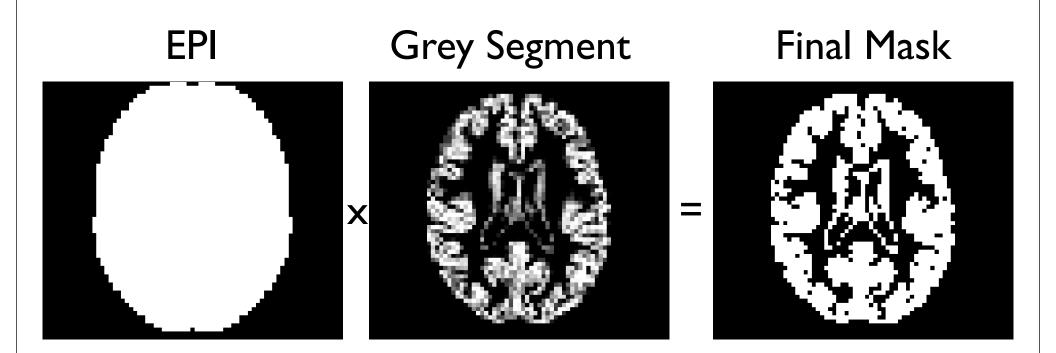


n Voxels : 93, Radius = 2.850000





# Result of using a EPI and grey mask



## Sample Preprocessing Effects on Time-series

For each stage the input is in black and the result is in red

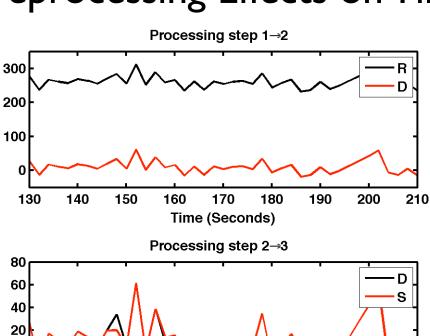
-20 -40

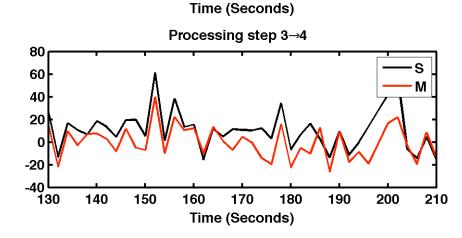
**130** 

140

150

160





170

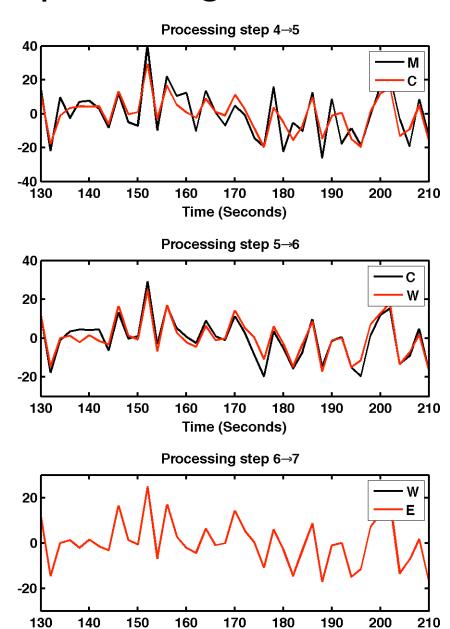
180

190

200

210

### Sample Preprocessing Effects on Time-series

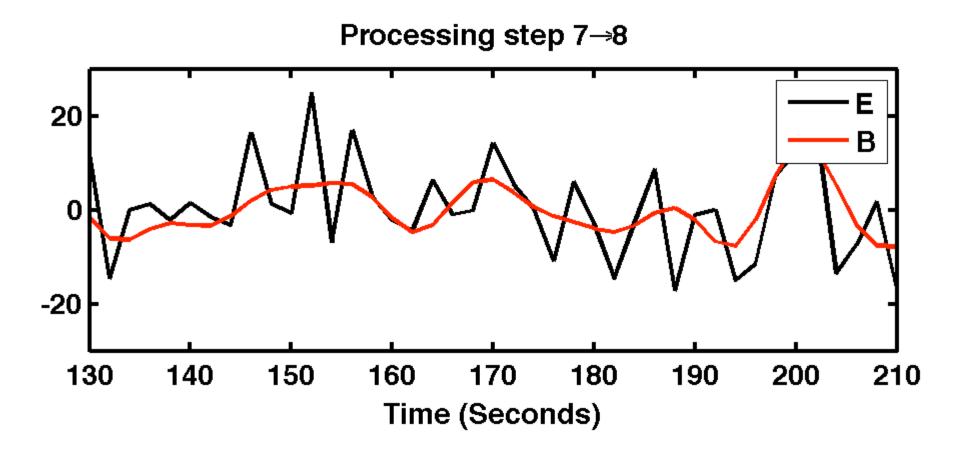


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Time (Seconds)

#### Sample Preprocessing Effects on Time-series



The final (red) time course is what is used for correlation calculations



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