New-ish AFNI Features:
a quick once-over

RW Cox, et al.
Autumn 2008

PDF Available as a News item at http://afni.nimh.nih.gov/afni

Outline

- 3dREMLfit = analysis allowing for serial correlation
- 3dLME = generalized ANOVA
- 1dGC = Granger Causality analysis
- align_epi_anat.py = align EPI and structural (T_1) datasets
- Miscellany
  - ★ Manganese MRI = tracing anatomical connectivity
  - ★ DCEMRI = Dynamic Contrast Enhanced MRI
  - ★ Realtime AFNI = feedback to the subject
  - ★ DTI = new plugin from UCSD
  - ★ ExamineXmat.R = analyze X matrix for potential problems

3dREMLfit

AFNI's New Approach to Dealing with Serial Correlation in FMRI Linear Regression (GLM)

3dREMLfit: Conclusions First

- Serial correlation does not appreciably impact the activation magnitudes (βs) estimated using **3dDeconvolve** (= Ordinary Least Squares solution)
- Group activation maps made from combining these βs using **3dANOVA**, **3dLME**, etc., are essentially the same using **3dDeconvolve** or **3dREMLfit** (= Generalized Least Squares solution)
  - ➢ In other words, **there is no need to re-run old group analyses** to see if allowing for serial correlation will change the results
- Thresholded individual subject activation maps are potentially affected, depending on the task timing and on the scanner
  - ★ The biggest effect of serial (AKA *temporal*) correlation—when this correlation is significant—is on the estimates of the ***variance*** of the individual subjects' βs
  - ★ If the variance is under-estimated using **3dDeconvolve**, then the individual subject t- and F-statistics will be over-estimated
  - ★ Individual subject variances and statistics are not usually carried forward to the group analysis level
    - o Since inter-subject variance is much larger than intra-subject variance
  - ★ Thus, group results are only marginally affected by serial correlation

`3dDeconvolve` and Ordinary Least Squares (OLSQ)

- OLSQ = consistent estimator of FMRI time series fit parameter vector β
  - ★ No matter what the temporal (AKA serial) correlation structure of the noise
    - o "Consistent" means that if you repeated the identical experiment infinitely many times, and averaged the estimated value (*e.g.*, β; variance), result would be the true value
- But OLSQ estimate of time series noise ***variance*** is not consistent when serial correlation is present
  - ★ OLSQ variance estimator will usually be biased too small with serial correlation
- Variance estimate is in denominators of formulas for t- and F-statistics
  - ★ Result: individual subject t- and F-values will be too large and/or their DOF parameters will be too large
  - ★ Upshot: Significance of individual subject activations will be over-estimated (p-values will be too small)
  - ★ Thresholded individual subject FMRI maps might show too much activation
  - ★ Obvious impacts on ROIs generated directly from individual subject activation maps (*e.g.*, for connectivity analysis)
  - ★ However, statistics taking into account serial correlation can be too conservative, and understate the extent of the "true" regions of activation
    - o For this reason, *and* to avoid selection bias, perhaps it is best to define FMRI-derived ROIs using a spherical "punch out" around each activation map peak

A Tiny Amount of Mathematics

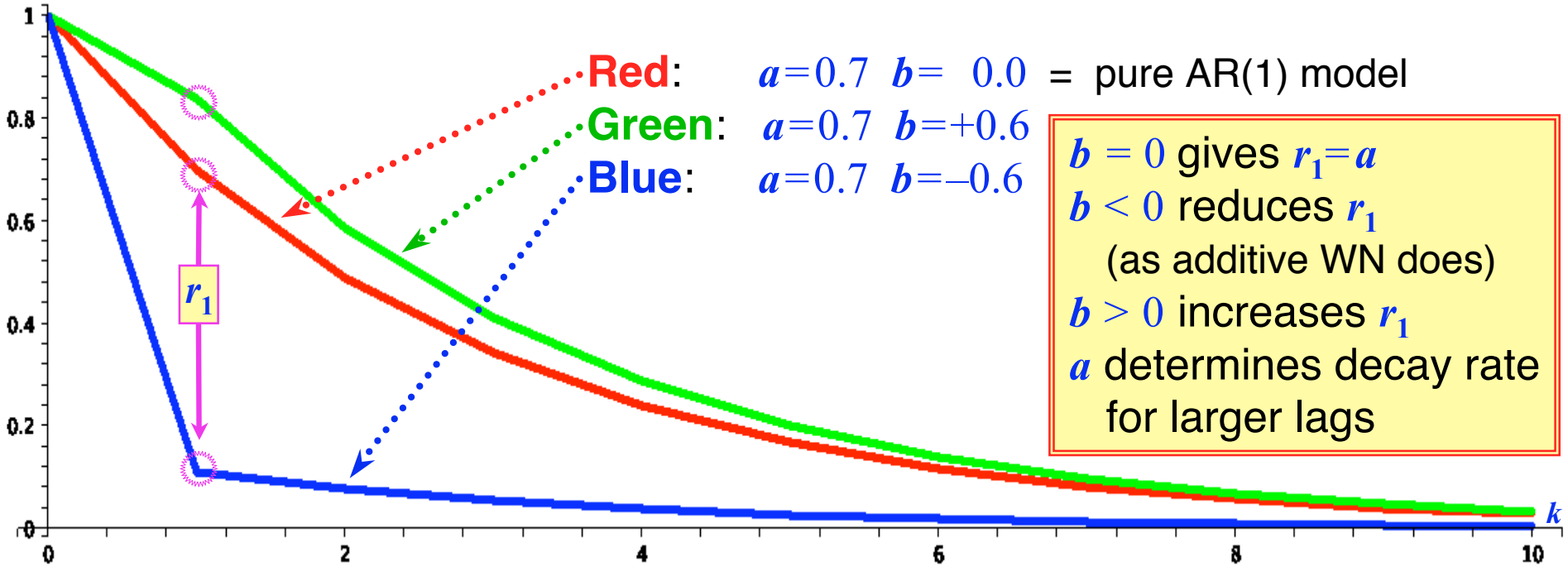
- White noise estimate of variance:

$$\hat{\sigma}^2 = \frac{1}{N-m}\sum_{i=0}^{N-1}[\text{data}_i - \text{fit}_i]^2$$

  - ★ N = number of time points; i = time index
  - ★ m = number of fit parameters
  - ★ $N-m$ = degrees of freedom (DOF) = how many equal-variance independent random values are left after the time series is fit with m regressors
    - o OLSQ assumption is that each of the N noise values in the data time series are equal-variance and independent (AKA white noise)
- If noise values *aren't* independent, then $N-m$ is too large an estimate of DOF, so variance estimate is too small
- Two possible solutions are:
  1) Adjust variance estimate (and so the t- and F-values) to allow for too few DOF
  2) Come up with a different variance estimator that has all $N-m$ DOF possible
     - o Requires estimating the temporal correlation structure of the noise as well
     - o Once temporal correlation matrix is known, use Generalized Least Squares (GLSQ; AKA pre-whitening) to estimate β parameter vector
     - o GLSQ is consistent and should produce β-values with smaller variance than OLSQ
- Solution #2 is what **`3dREMLfit`** implements

Mathematical Model for Serial Correlation

- My choice: ARMA(1,1) = **A**uto**R**egressive order 1 **+** **M**oving **A**verage order 1
  - ★ Notation: r_k = correlation at time lag #k for k=1,2,…,N-1
- parameter a = decay rate of the r_k as k increases: for FMRI, $0 \le a < 1$
- parameter b = affects correlation at lag 1 (r_1): $-1 < b < 1$
  - ★ $r_1 = (a+b)\cdot(1+a\cdot b)/(1+2a\cdot b+b^2)$ $r_k = a^{k-1} r_1$ for $k = 1,2,...$
- For $a > 0$ and $-a < b < 0$, ARMA(1,1) noise can be thought of as a sum of AR(1) noise and white noise, with variance proportions determined by b
  - ★ Why I prefer 2 parameter ARMA(1,1) over easier 1 parameter AR(1) model (b=0)



New Program: `3dREMLfit`

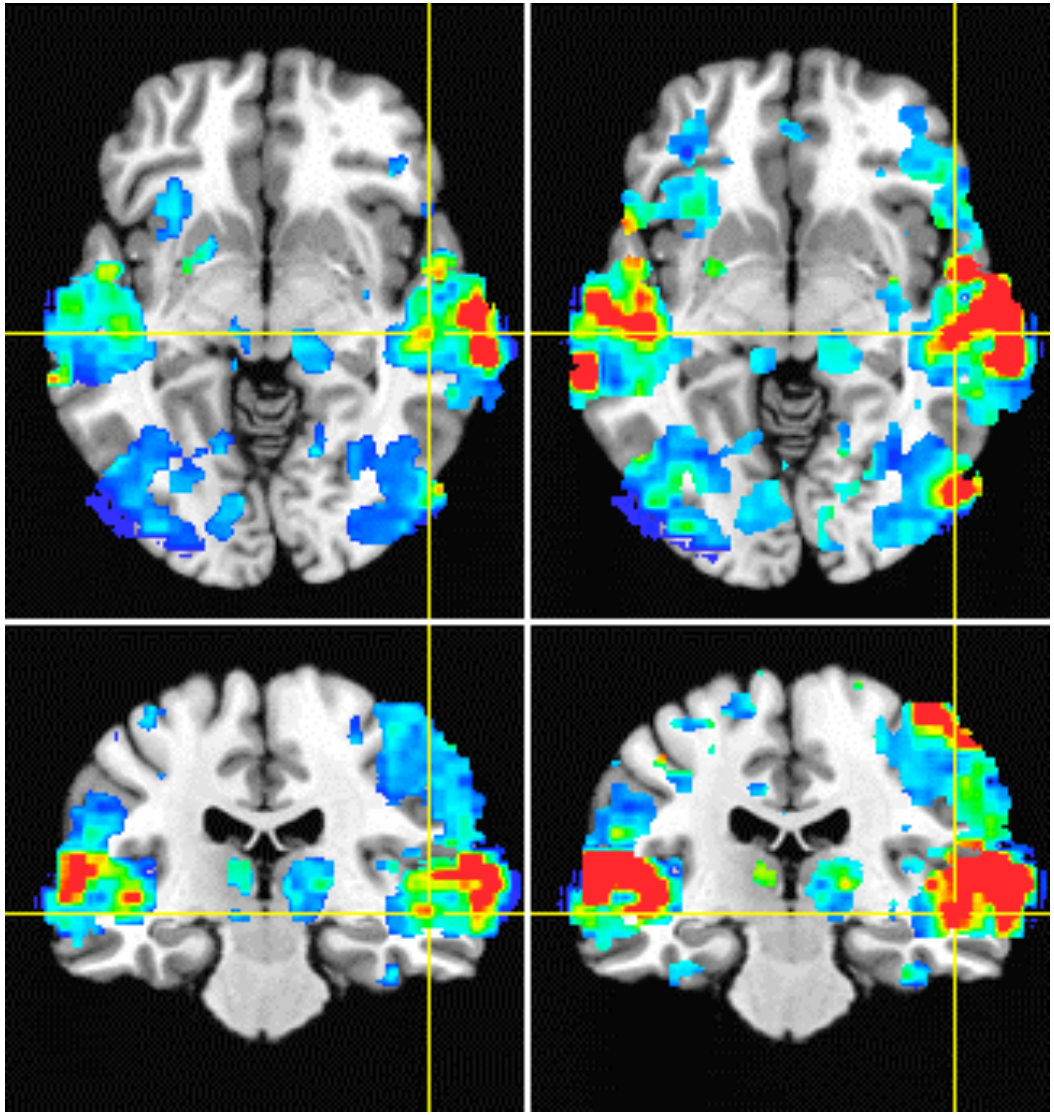
- Implements Solution #2: estimate correlation parameters and use GLSQ
  - ★ **REML** is a (partially nonlinear) method for simultaneously estimating variance + correlation parameters ***and*** estimating regression fit parameters (βs)
  - ★ *Each voxel* gets a separate estimate of its own correlation parameters (a,b)
    - o Estimates of a and b can be spatially smoothed before they are used to compute the βs
    - o Can also input a and b directly and skip their estimation (the slow part), if desired, and use *those* values to compute the βs
    - o Variance estimate uses pre-whitened residuals to keep DOF=$N-m$
  - ★ Even if correlation decay parameter a was the same for all voxels, relative amount of white noise (measured by b) mixed in would vary spatially
    - o Sample analyses using 1-parameter AR(1) and MA(1) models shown later
- Inputs to `3dREMLfit`
  - ★ Run `3dDeconvolve` first to setup `.xmat.1D` matrix file, GLTs, etc.
    - o Don't have to let `3dDeconvolve` finish analysis: `-x1D_stop`
    - o `3dDeconvolve` also outputs a command line to run `3dREMLfit` with the same 3D+time dataset and the matrix file just created
  - ★ Then, input matrix file and 3D+time dataset to `3dREMLfit`
- Output datasets are structured to be similar to those in `3dDeconvolve`
  - ★ It should be easy to adapt scripts that use `3dDeconvolve` output files (*e.g.*, for group analysis) to use the new software

Rapid Event Related Design (NIH 3 T: JJY)

Individual Maps from 17 Subjects

- Color map & Threshold**:** Full F such that p=0.001 (Underlay = TT_N27+tlrc)

REML
F=3.35
p=0.001



OLSQ
F=3.35
p=0.001

GIF Animation:
time = subject
Not visible in PDF

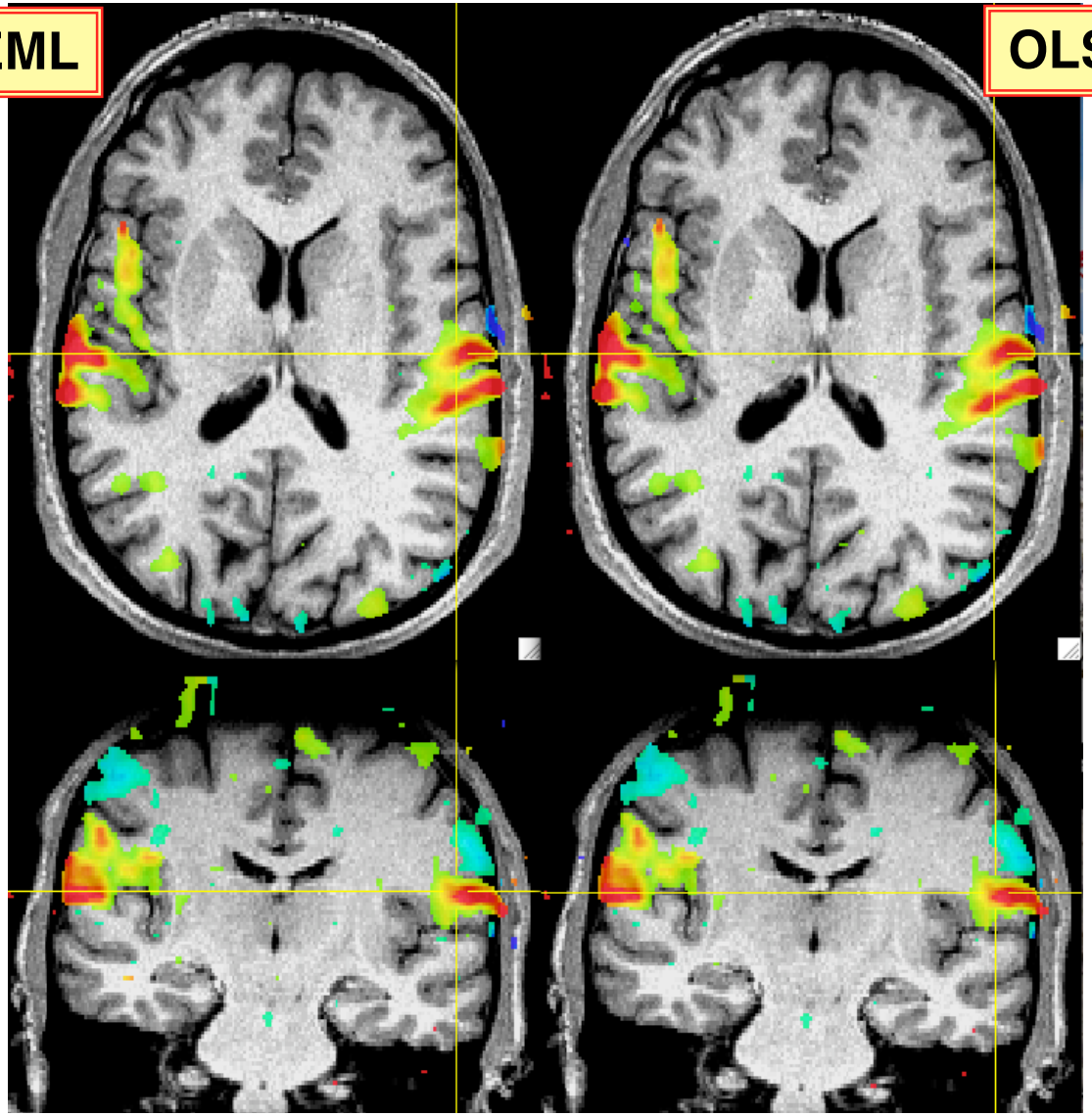
Differences between REML and OLSQ are noticeable with rapid event-related design (but activated regions are very similar)

Block Design (15 s blocks: FBIRN-1 SM Task)

1 **Individual** Map (Subject#106)

Color=% signal change; Threshold: p=0.05 (uncorrected)

REML **OLSQ**



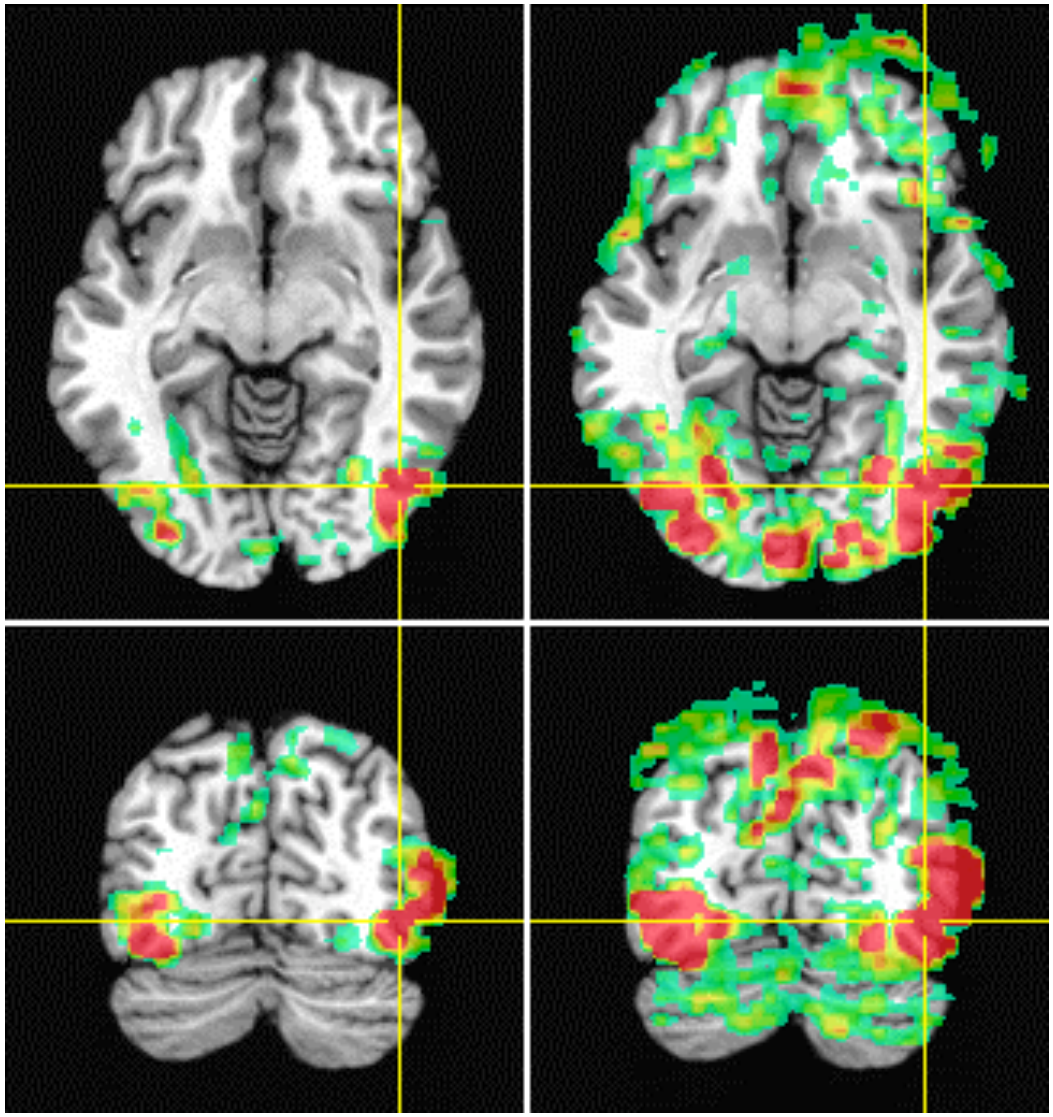
- Very little difference between OLSQ and REML, even at so low a threshold
- Data is markedly less correlated in time (UNM Siemens 1.5 T), as shown by maps of REML-estimated r_1
- Similar data from U Iowa GE 1.5 T has similarly low temporal correlation
- BWH & MGH 3 T data has higher temporal correlation than FBIRN 1.5 T, but lower than NIH 3 T —— **???**

Block Design (30 s blocks: NIH 3T; JJY)

Individual Maps from 16 Subjects

- Color map & Threshold**:** Full F such that p=0.001 (Underlay = TT_N27+tlrc)

REML
F=3.15
p=0.001



OLSQ
F=3.15
p=0.001

GIF Animation:
time = subject
Not visible in PDF

This is the **worst situation** for OLSQ: stimulus is at very low frequencies, where noise correlation affects variance the most

Results Thus Far

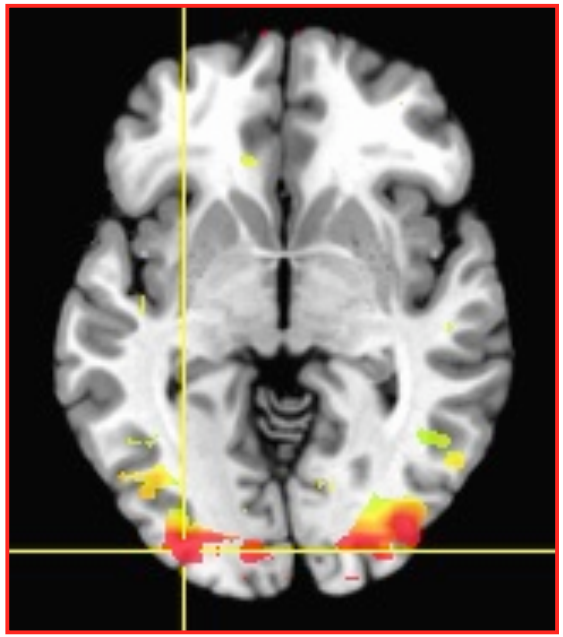
- Between OLSQ and GLSQ+REML:
  - ★ Individual subject thresholded activation maps may differ very little, some, or a lot
- Level of temporal correlation determines how much difference GLSQ makes to individual subject statistics
  - ★ Amount of temporal correlation seems to depend on magnetic field strength, other scanner details, pulse sequence, …
  - ★ Effect of temporal correlation also seems to depend on stimulus timing
  - ★ As theory indicates:
    - o Temporal correlation means noise variance depends on frequency
    - o So amount of noise that interferes with ("looks like") the signal will depend on frequencies at which the hemodynamic response is appreciable
- Next slides: Group activation maps, GLSQ+REML vs OLSQ
  - ★ 2 cases from NIH: Event-related and Block:30s designs
  - ★ Don't have enough FBIRN-1 subjects to do a group analysis

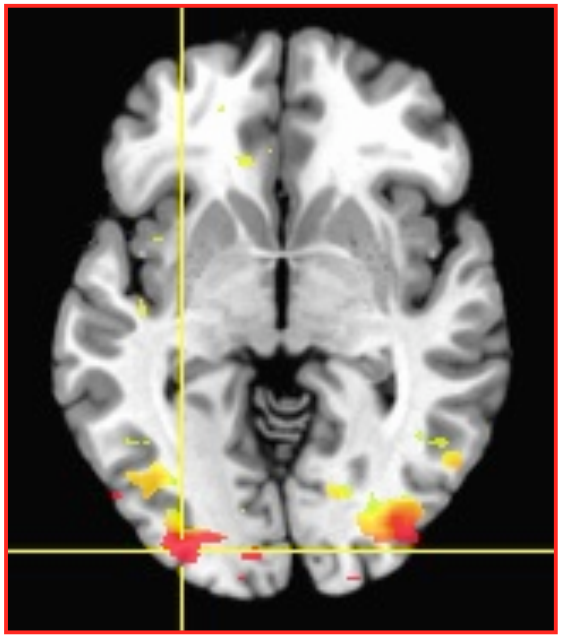
Block Design: Group Results (3dANOVA3)

REML

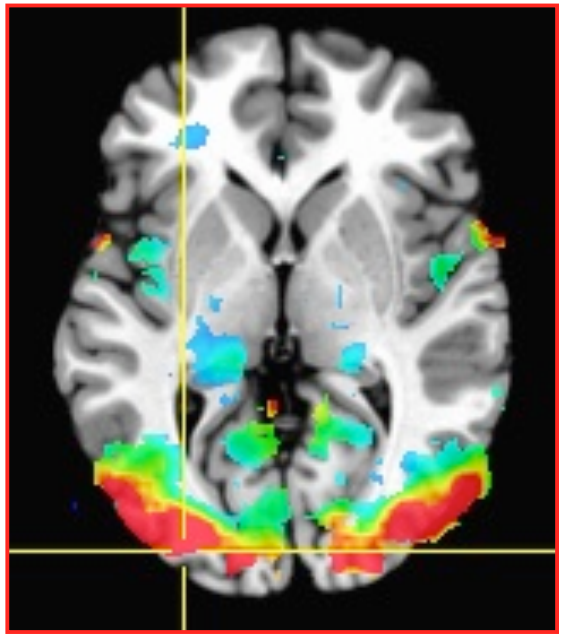
OLSQ

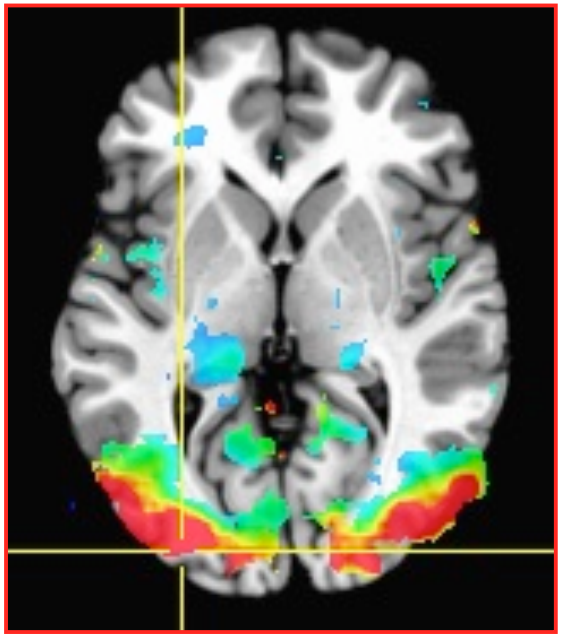
***F*-test for Affect condition**





***F*-test for Category condition**



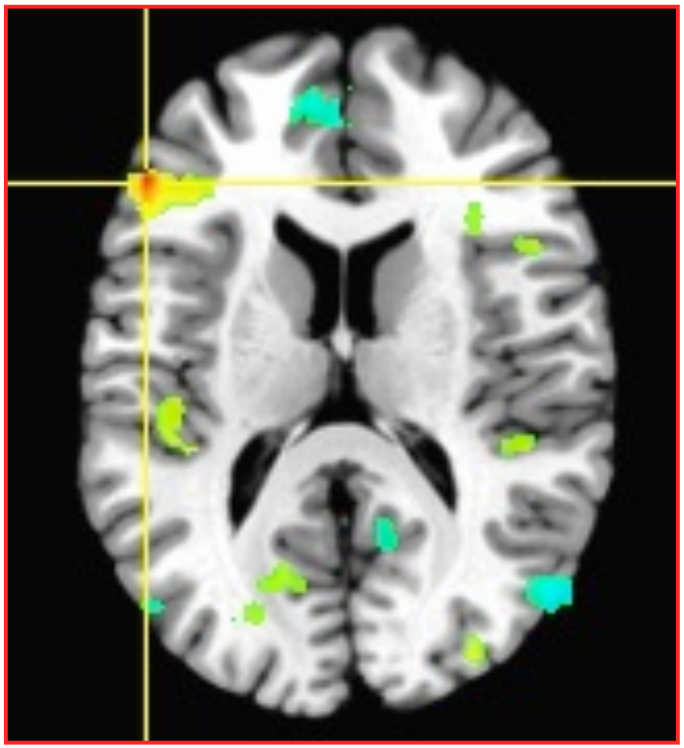


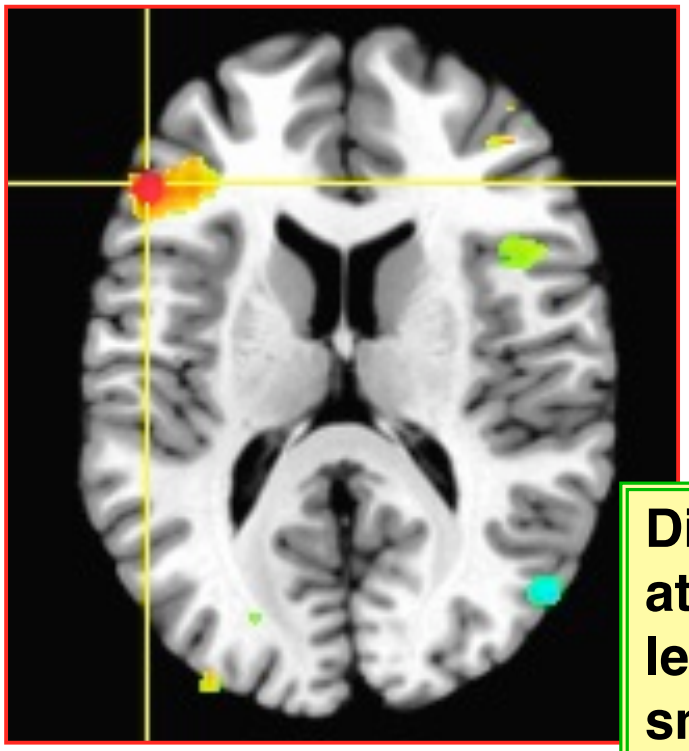
Differences at group level are small:

∃ Many false negatives in individual maps when using more conservative GLSQ+REML**?**

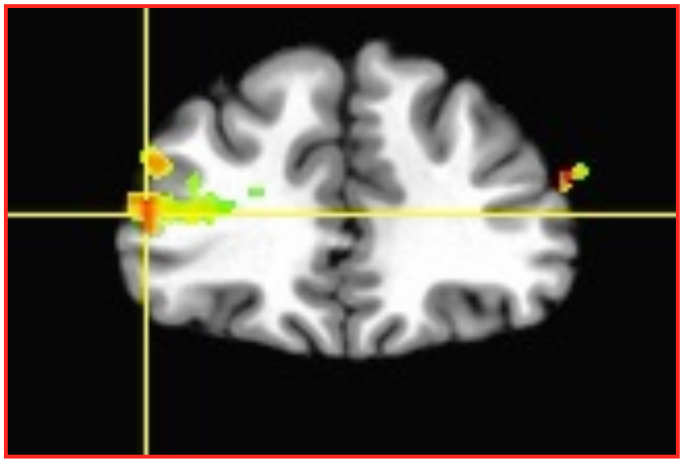
Event-Related Design: Group Results (3dANOVA3)

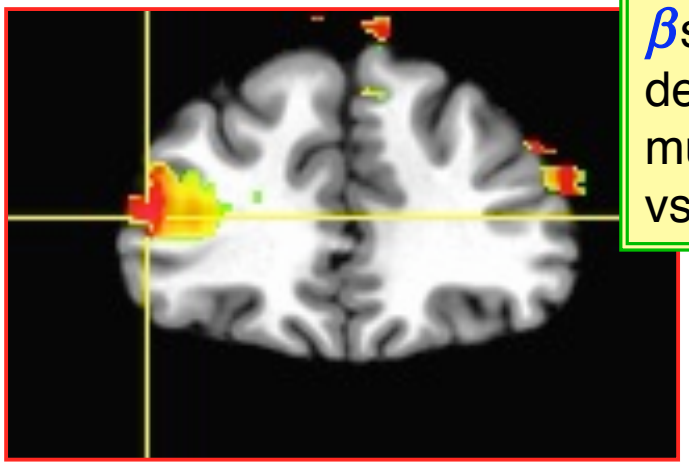
REML





OLSQ





Differences at group level are small:

βs don't depend very much on REML vs OLSQ

Tentative Conclusions

- For individual subject thresholded activation maps:
  - ★ Use GLSQ/REML estimation, especially for slow block design experiments at 3+ Tesla
  - ★ Be aware that there may be many false negatives
    - o i.e., false acceptances of the null hypothesis
    - o am looking into an FDR-like procedure for estimating the missed detection rate, similar to how FDR estimates the false positive rate
- For group maps using ANOVA (or similar statistics):
  - ★ Differences between OLSQ and GLSQ estimation are small
- Recommendations:
  - ★ **Don't need to re-visit group activation conclusions*!***
  - ★ Use **`3dREMLfit`** as a near drop-in replacment for **`3dDeconvolve`** for future work
    - o A little extra CPU time (usually from 1..3 times as long)

Outline of SPM and FSL Approaches

- SPM5 and SPM2
  - ★ Estimate fixed **ARMA(1,1)** (more precisely, AR(1)+white noise) model for all "voxels of interest" (pass an OLSQ F-test)
    - o By averaging estimated auto-covariance matrix from OLSQ residuals over these voxels
    - o SPM assumes AR parameter $a \approx 0.2$, and approximates ARMA(1,1) correlations via linear Taylor series, to make correlation parameter estimation easier to program
  - ★ Use GLSQ (same for each voxel) to solve for βs
    - o SPM99: Use OLSQ and adjusts DOF downwards to allow for serial correlation
- FSL and FMRIstat (similar, but differ in important details at several points)
  - ★ Use OLSQ to get first-pass residuals; use these to estimate each voxel's auto-correlation matrix; smooth these matrices spatially (FSL & FMRIstat vary here)
  - ★ Estimate **AR(1)** parameter for each voxel separately from smoothed matrices
  - ★ Use GLSQ (different for each voxel) to solve for βs
- All these programs use a non-REML method to estimate serial correlation parameter(s) from the OLSQ residual auto-correlation matrix, and then adjust these estimates to reduce the bias thus introduced

Using 3dREMLfit - 1

- Step 1: run **3dDeconvolve** as normal, setting up timing, GLTs
- **3dDeconvolve ... -bucket Adecon -x1D_stop**

filename re-used for **3dREMLfit** command

Screen output:

```
++ Wrote matrix values to file Adecon.xmat.1D
++ ========= Things you can do with the matrix file =========
++ (a) Linear regression with ARMA(1,1) modeling of serial
 correlation:

3dREMLfit -matrix Adecon.xmat.1D -input ss17.AllRuns.norm+orig
 -mask ss17_mask+orig -Rbeta Adecon_beta_REML -fout -Rbuck
 Adecon_REML -Rvar Adecon_REMLvar

++ N.B.: 3dREMLfit command above written to file Adecon.REML_cmd
++ (b) Visualization/analysis of the matrix via ExamineXmat.R
++ (c) Synthesis of sub-model datasets using 3dSynthesize
++ ================================================
++ 3dDeconvolve exits: -x1D_stop option was given
```

Using 3dREMLfit - 2

- Step 2: run **3dREMLfit** ; perhaps adding options to the command line:
  - ★ **-addbase** : add extra baseline columns to the regression matrix
  - ★ **-slibase** : add extra baseline columns to the regression matrix, ***on a per slice basis*** = intended to aid in removal of physiological noise
  - ★ **-gltsym** : add extra GLTs (beyond those from **3dDeconvolve**)
  - ★ **-usetemp** : **-slibase** can require a lot of memory
    - o Generates REML matrices for many (a,b) cases for each slice
    - o This option writes & reads temporary matrices to disk to reduce RAM usage
      - ➥ **-verb** : outputs information about memory usage as program runs
  - ★ **-Obuck** : output OLSQ bucket dataset (etc.)
    - o **-Rbuck** : output GLSQ bucket (stimulus βs and statistics)
    - o **-Rbeta** : output GLSQ (all the βs and only the βs; no statistics)
    - o **-Rfitts** : output GLSQ fitted model
    - o **-Rvar** : output GLSQ (a,b) parameters and variance estimate (per voxel)
  - ★ **-NEGcor** : allow negative correlations in the estimation
    - o Probably not really needed for FMRI, but option is there just in case
    - o There are more options to control estimation of the (a,b) parameters
- **Of course**: read the output of **3dREMLfit -help**

Potential Add-ons to **3dREMLfit**

- Add option to use this program to **afni_proc.py** super-script
- Add **-iresp** and **-sresp** options
- Output variances for βs
  - ⋆ *e.g.*, to be carried to the group analysis level? Need to implement a new approach for this option to be useful.
- Matrix error checking when **-addbase** or **-slibase** is used
  - ⋆ In case the bumbling user puts in a collinear column
  - ⋆ Program cannot handle an all-zero column (unlike **3dDeconvolve**)
- Re-run with extra GLTs to be added to existing bucket
  - ⋆ Or at least have a GLT-only output option: **-Rglt** ??
- Finish work with **R Birn**'s physiological noise regressors and integrate these into time series analysis via **-slibase**
- **-jobs** option to spread load across multiple CPUs
  - ⋆ Especially loop where parameters (a,b) are estimated: the slowest part
- … ???

Next: more details on ARMA vs AR vs MA

Serial Correlation Model & Notation: ARMA(1,1)

- Denote noise value at time index i by ξ_i for i=0..N–1
- Variance is average (AKA expected) value of noise squared:
  - ★ $\sigma^2 = E[\xi_i^2]$ where $E[\bullet]$ means "expected value of •"
- Covariance is similar to variance, measured between different time points:
  - ★ $\Sigma_{|i-j|} = E[\xi_i \xi_j]$ which depends on time *difference* between time points i and j
- Correlation is covariance with variance factored out
  - ★ $E[\xi_i \xi_j] = \sigma^2 r_{|i-j|}$ (with r_0=1)
    - o N.B.: r_k measures predictability of noise value at time j+k given value at time j
- For entire time series, express variance/correlation as a matrix
  - ★ $E[\xi \xi^T] = \sigma^2 \mathbf{R}$ with correlation matrix $\mathbf{R}$ having elements $R_{i,j} = r_{|i-j|}$
- Need to have a simplified model for $\mathbf{R}$ (*i.e.*, the r_k for k=1,2,…,N-1)
  - ★ Otherwise, have too many parameters to estimate
  - ★ My choice: ARMA(1,1) = **A**uto**R**egressive order 1 + **M**oving **A**verage order 1
  - ★ parameter a = decay rate of the r_k as k increases: for FMRI, $0 \le a < 1$
  - ★ parameter b = determines correlation at lag 1 (r_1): $-1 < b < 1$
    - o $r_1 = (a+b)\cdot(1+a\cdot b)/(1+2a\cdot b+b^2)$ $r_k = a^{k-1} r_1$ for $k = 1,2,...$
  - ★ For $a > 0$ and $-a < b < 0$, ARMA(1,1) noise can be thought of as a sum of AR(1) noise and white noise, with variance proportions determined by b
    - o This feature is one reason I prefer ARMA(1,1) as a noise correlation model over AR(1)

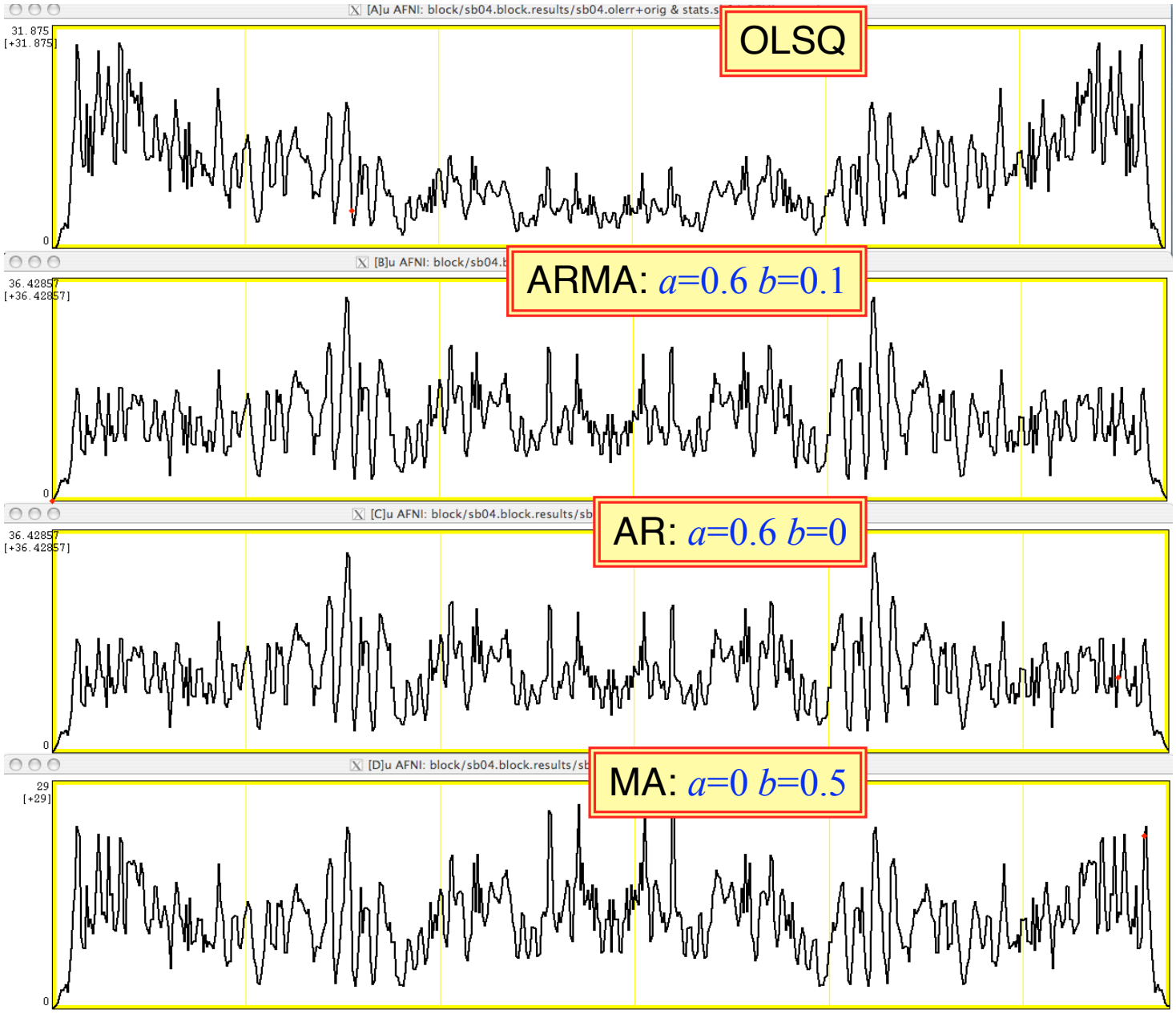
AR(1): a vs. MA(1): b vs. ARMA(1,1): a & b

- Check the effectiveness of GLSQ pre-whitening solution by examining pre-whitened residuals
  - ⋆ Pre-whitening: applying a linear transformation to the time series data to de-correlate the noise
    - o Symbolically, $\mathbf{R}^{-1/2}$ where $\mathbf{R}$ is the correlation matrix
- After pre-whitening, residuals (difference between data and fitted time series) should be (mostly) uncorrelated
- Power spectrum of white noise is flat
  - ⋆ Power spectrum = expected value of absolute value of Fourier transform, averaged over an infinity of repeated identical experiments
- Visually inspect graph of abs[FFT(pre-whitened residuals)]
  - ⋆ Should be flattish, with random excursions
    - o This is noise, after all, and we don't have an infinity of data over which to average
- Next 4 slides:
  - ⋆ Graphs of "spectrum" for OLSQ and GLSQ using ARMA(1,1), AR(1), and MA(1) correlation models (generated using interactive AFNI, of course)
  - ⋆ For 3 strongly "active" voxels in one subject (block design: 30 s blocks; NIH 3T)
  - ⋆ Then the single subject activation maps for 6 types of analysis

Spectrum (slightly smoothed absFFT) of Residuals

In this voxel:

- **OLSQ**: definitely not "white"
- **GLSQ**: "white-ish" for all 3 correlation models

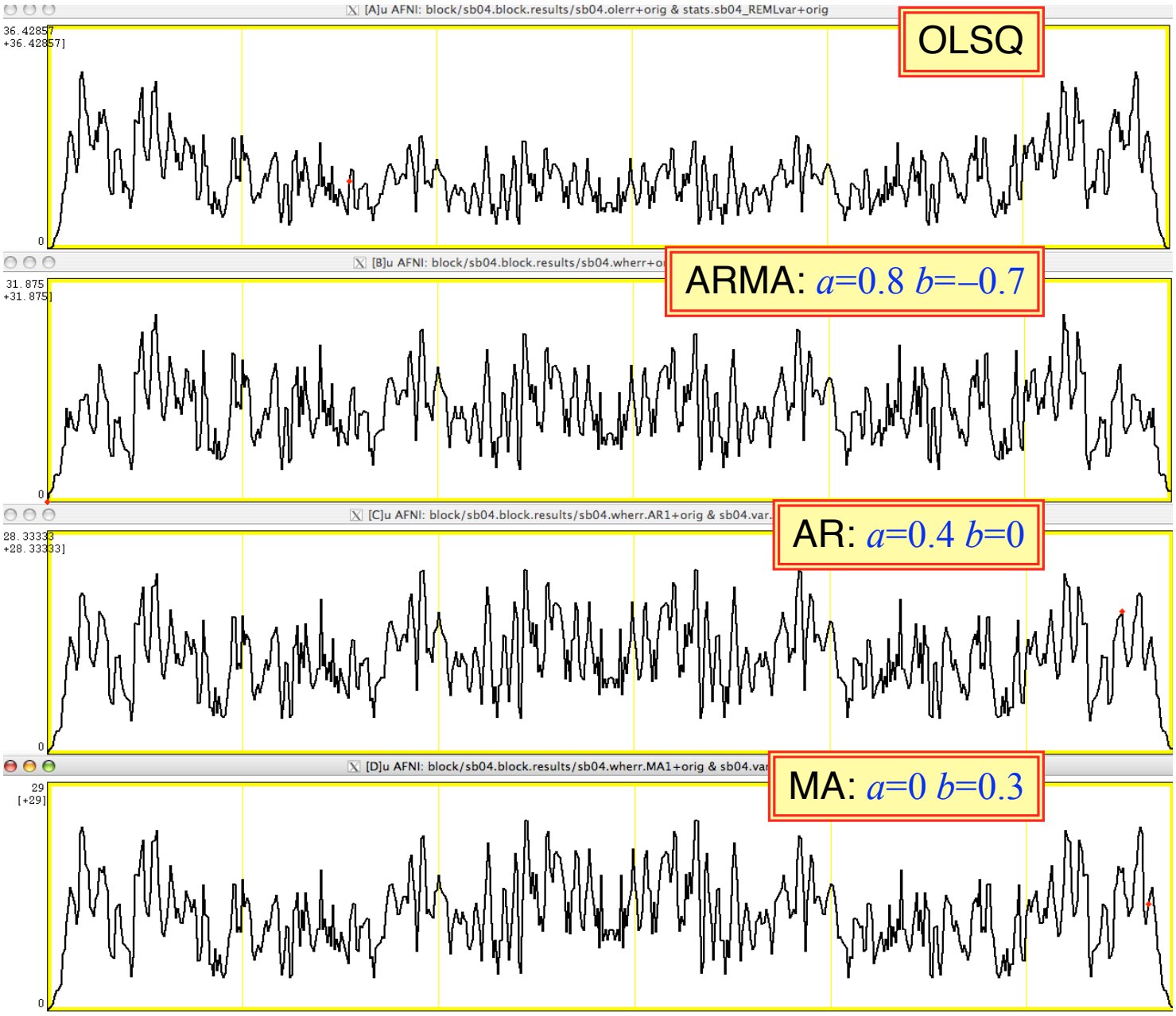


Block:30s

Spectrum of Residuals

In this voxel:

- **OLSQ**: not "white" but not very "colored" either
- **GLSQ**: All methods about the same in fixing up what little needs to be fixed

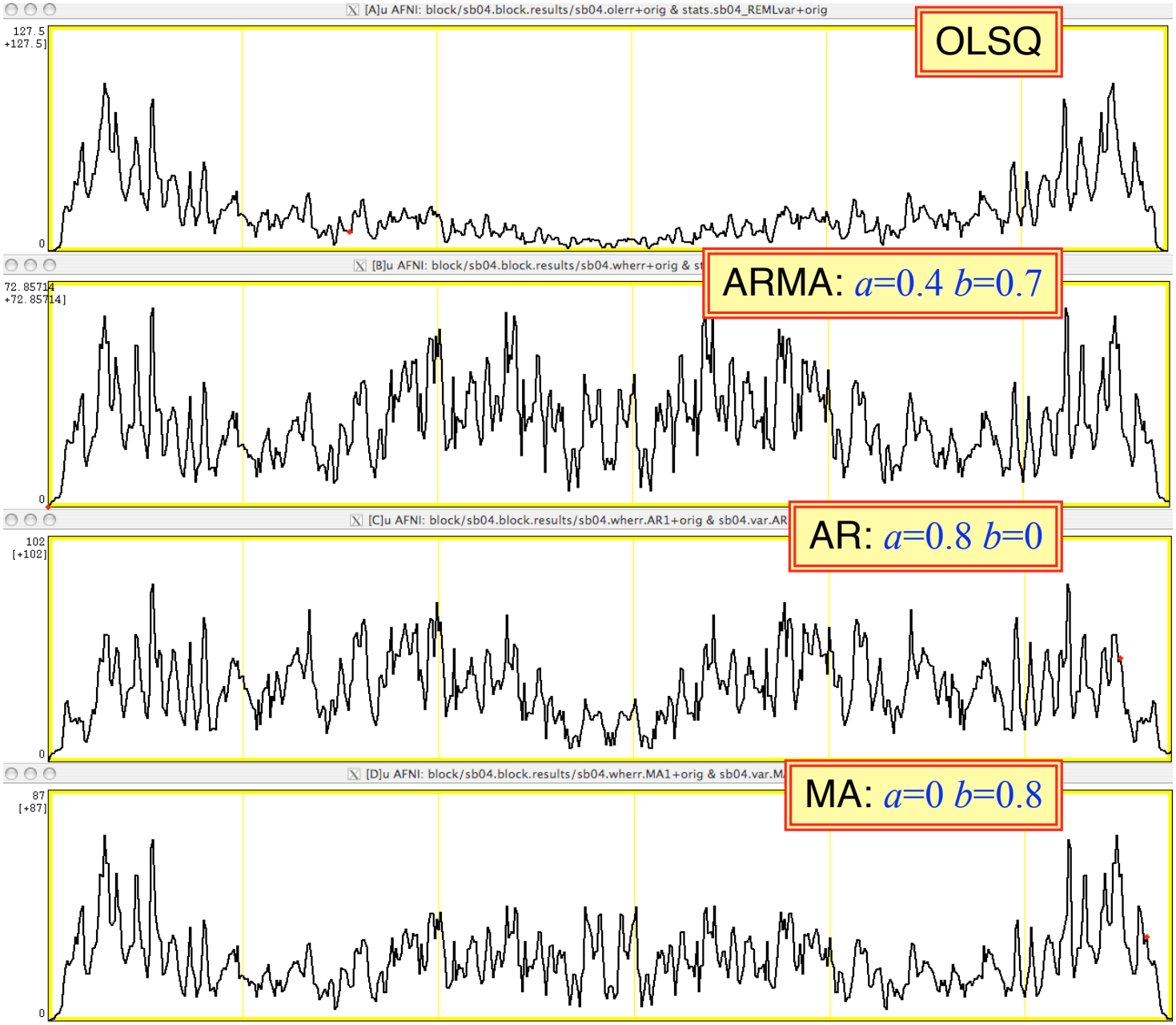


Block:30s

Spectrum of Residuals

In this voxel:

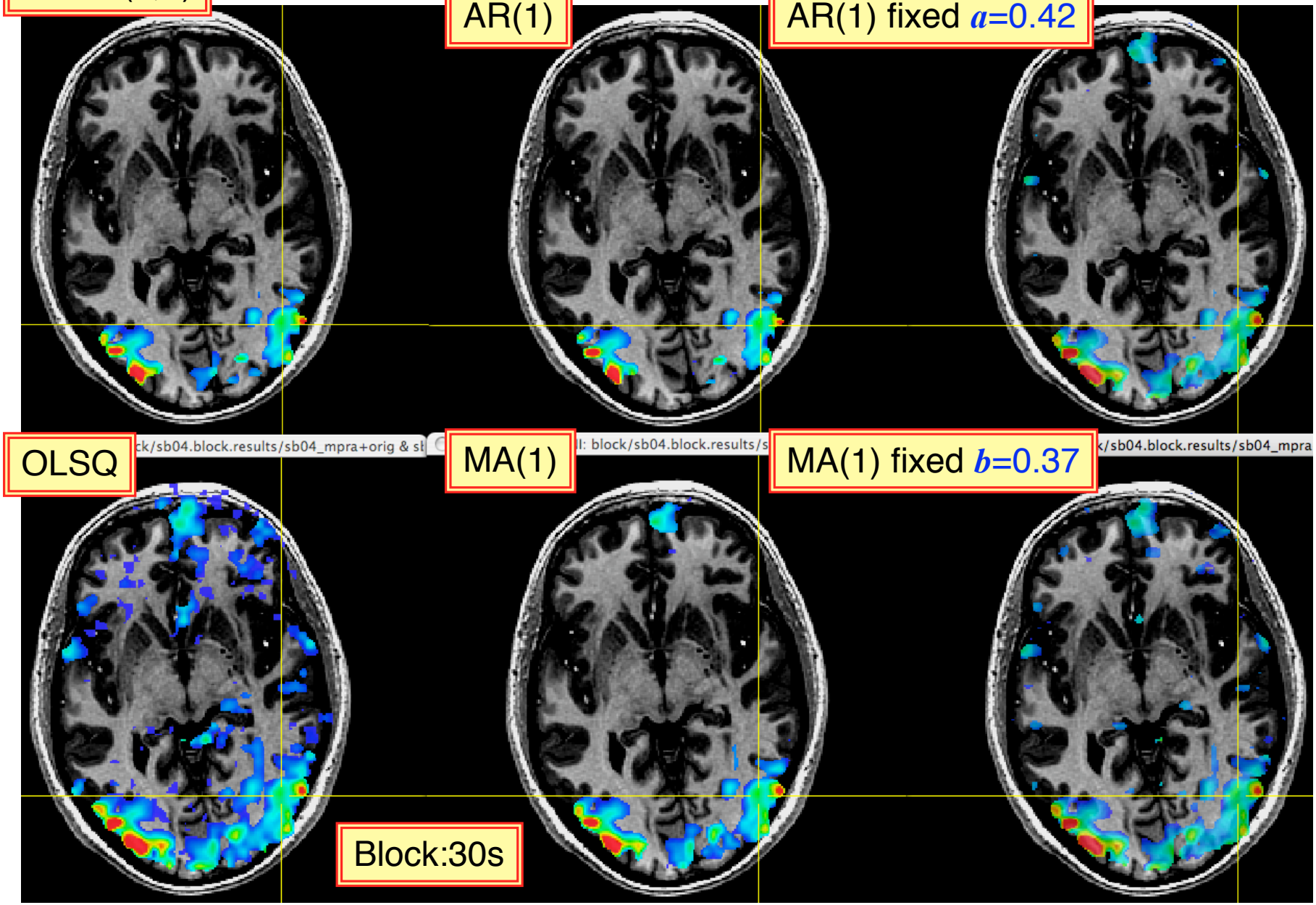
- **OLSQ**: definitely not "white"
- **GLSQ**: ARMA appears a little "whiter" than either AR or MA alone



Block:30s

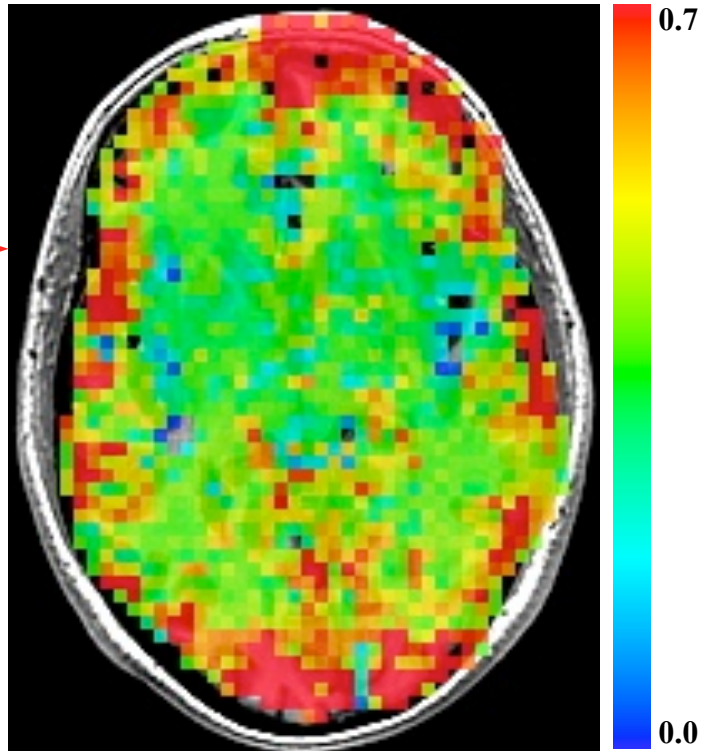
6 Types of Analysis

Threshold=F
Color=$\beta_{task\#1}$



Conclusions from Previous Slides

- It is possible to find voxels where pre-whitening of different types (AR-only or MA-only or ARMA) is "optimal"
  - ★ And voxels where pre-whitening makes little difference
- For many (most?) voxels, the pre-whitening details don't make a lot of difference in the statistics
  - ★ As long as *something* is done that is about right
  - ★ *e.g.*, Using fixed AR(1) or MA(1) single parameter method was still OK-ish for single subject maps
    - o A few more extraneous small blobs
    - o But fewer than pure OLSQ solution statistics
- Map of r_1=correlation at neighboring TRs, as output by REML and ARMA(1,1) fit
  - ★ Same slice as previous slides (NIH 3 T data)
  - ★ In general, cortical gray matter shows more correlation, but this result is not universal



Mathematics and Implementation

- Available in PDF (scanned from hand-written pages) for the truly devoted
  - ★ File **3dREMLfit_mathnotes.pdf**
- Outline of REML estimation methodology
  - ★ What is REML and why do we care?
- Matrix algebra for efficient solution of the many linear systems that must be solved for each voxel
  - ★ Sparse matrix factorizations, multiplications, and solvers
- How ARMA(1,1) parameters are estimated in **3dREMLfit**
  - ★ Optimizing REML log-likelihood function over a discrete grid of (a,b) values, using 2D binary search
  - ★ Must solve a GLSQ problem for each (a,b) tested, for each voxel
- How statistics are implemented as GLTs
  - ★ Testing null hypothesis $\mathbf{G}\boldsymbol{\beta}=0$ for arbitrary matrix $\mathbf{G}$
- Derivation of ARMA(1,1) formulas
  - ★ For completeness, and because we all *love* equations

3dLME

Group Analysis Beyond the Capabilities of ANOVA

Linear Mixed-Effects Modeling: 3dLME

- Limitations of traditional group analysis with ANOVA:
  - ★ Usually requires equal number of subjects across groups
  - ★ Doesn't allow missing data from individual subjects
    - o If a subject didn't perform a task, have to throw away all the data from the subject?
  - ★ Allows only a limited number of factors and fixed design structures
    - o **3dANOVAx**: Currently only allows up to 4 fixed factors
  - ★ Cumbersome when modeling HRFs with multiple basis functions
    - o Use area under the curve (AUC)?
    - o Difficult to detect shape difference
    - o Troubling when undershoots occur
  - ★ Inflexible when handling residual variance-covariance structure
    - o Strong assumptions: homoscedasticity and sphericity
  - ★ Model fine-tuning impossible
    - o Even if an interaction is insignificant, it has to stay in the model
    - o Unwieldy with covariates
- Linear mixed-effects (LME) modeling comes to save the day

Linear Mixed-Effects Modeling: `3dLME`

- Program `3dLME`
  - ★ Written in open source language R
  - ★ Fills in the gaps in ANOVA's repertoire
  - ★ Batch mode with all specifications included in text file `model.txt`
  - ★ See **http://afni.nimh.nih.gov/sscc/gangc/lme.html** for more information
  - ★ Downsides
    - o High computational cost: lots of calculation; R isn't so efficient
    - o Some statistical controversies about DF's and F-statistic (sequential vs. marginal)
- When HRF is modeled with multiple basis functions
  - ★ Reassemble HRF's (unnecessary with TENT or CSPLIN)
  - ★ Assume amplitudes of an HRF at k equally-spaced time points: $\boldsymbol{\gamma}_1$, $\boldsymbol{\gamma}_2$,… $\boldsymbol{\gamma}_k$
  - ★ We don't care about the differences among $\boldsymbol{\gamma}$'s, so won't test H_0: $\boldsymbol{\gamma}_1=\boldsymbol{\gamma}_2=\ldots=\boldsymbol{\gamma}_k$
  - ★ Instead we want to focus on H_0: $\boldsymbol{\gamma}_1=\boldsymbol{\gamma}_2=\ldots=\boldsymbol{\gamma}_k=0$
  - ★ And have to deal with temporal correlations among $\boldsymbol{\gamma}$'s

Linear Mixed-Effects Modeling: 3dLME

- 1st example of **model.txt**
  - ★ 3 fixed factors: gender, object, and modality; 1 covariate: age
  - ★ Gender: male and female; Object: face and house; Modality: visual and audial

```
Data:Volume                              <-- either Volume or Surface
Output:FileName                          <-- any string (no suffix needed)
MASK:Mask+tlrc.BRIK                      <-- mask dataset
Model:Gender*Object*Modality+Age         <-- model formula for fixed effects
COV:Age                                  <-- covariate list
RanEf:TRUE                               <-- random effects
VarStr:0                                 <-- variance structure
CorStr:0                                 <-- correlation structure
SS:sequential                            <-- F-statistic: sequential or marginal
MFace-FFace                              <-- contrast label
Male*Face*0*0-Female*Face*0*0            <-- contrast specification
MVisual-Maudial
Male*0*Visual*0-Male*0*Audial*0
......
```

Subj	Gender	Object	Modality	Age	InputFile
Jim	Male	Face	Visual	25	file1+tlrc.BRIK
Carol	**Female**	**House**	**Audial**	**23**	**file2+tlrc.BRIK**
Karl	Male	House	Visual	26	file3+tlrc.BRIK
Casey	Female	Face	Audial	24	file4+tlrc.BRIK

```
......
```

  - ★ Command: **3dLME.R MyOutput &**

Linear Mixed-Effects Modeling: 3dLME

- 2nd example of **model.txt**
  - ★ HRF modeled with 6 tents; H_0: $\beta_1=\beta_2=\ldots=\beta_6=0$

```
Data:Volume                                  <-- either Volume or Surface
Output:FileName                              <-- any string (no suffix needed)
MASK:Mask+tlrc.BRIK                          <-- mask dataset
Model:Time-1                                 <-- model formula for fixed effects
COV:                                         <-- covariate list
RanEf:TRUE                                   <-- random effects
VarStr:0                                     <-- variance structure
CorStr:1_Order|Subj                          <-- correlation structure
SS:sequential                                <-- F-statistic: sequential or marginal
Subj      Time    TimeOrder   InputFile
Jim       t1        1         JimT1+tlrc.BRIK
Jim       t2        2         JimT2+tlrc.BRIK
......
Jim       t6        6         JimT6+tlrc.BRIK
Carol     t1        1         CarolT1+tlrc.BRIK
Carol     t2        2         CarolT2+tlrc.BRIK
......
Carol     t6        6         CarolT6+tlrc.BRIK
......
```

  - ★ Command: **3dLME.R MyOutput &**
  - ★ Output: an F for H_0, β and t for each basis function

1dGC

Granger Causality Analysis (and other connectivity tools)

Granger Causality Analysis: `1dGC`

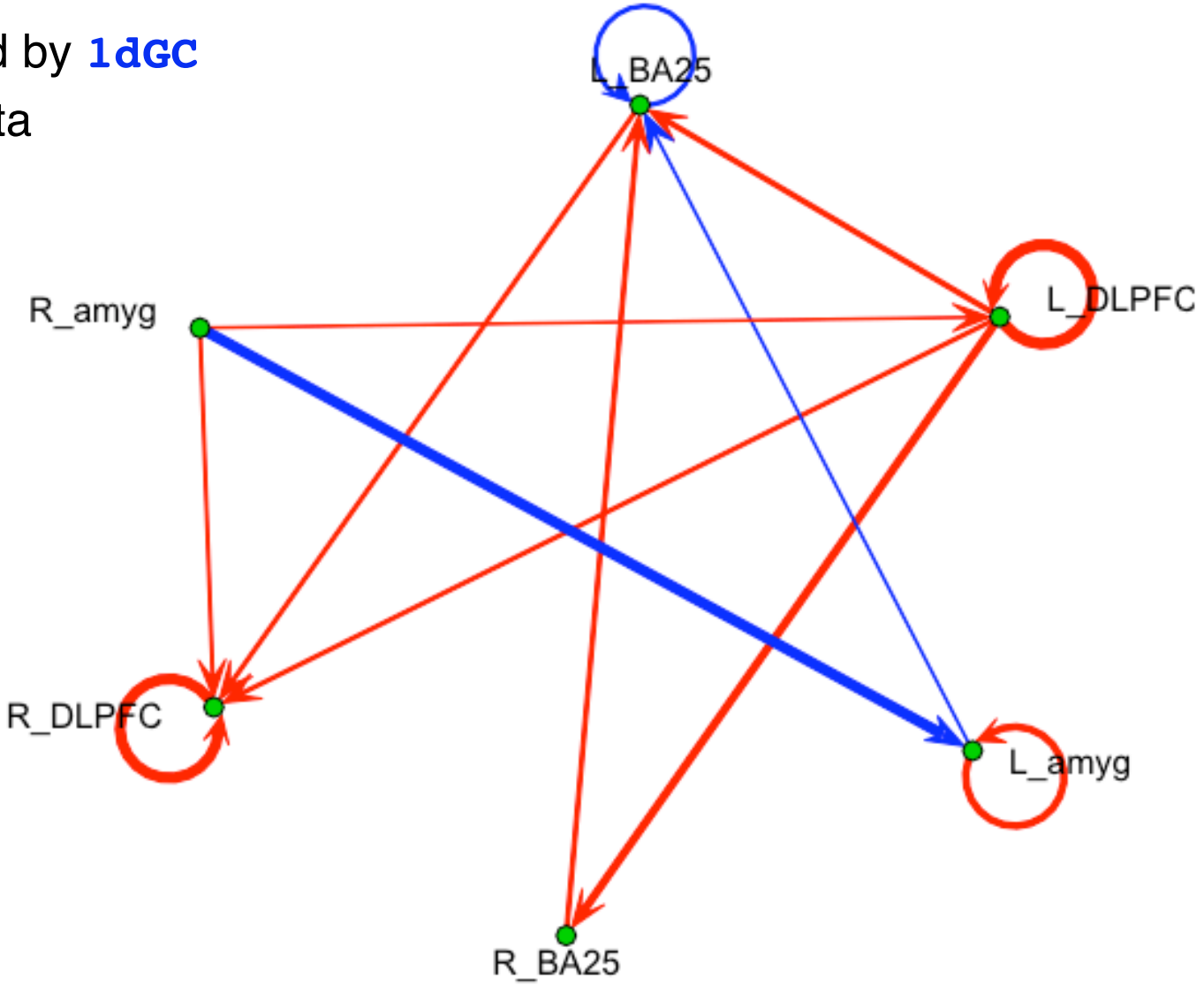
- Network detection in the brain
  - ★A network in the brain may leave some signature (e.g., latency) in the fine texture of BOLD signal because of dynamic interactions among regions
  - ★Reverse engineering: such a signature may reveal the network structure
  - ★Assumption: causes precede effects, or latencies indicate causal relationship
  - ★Problem: some latency effects might be due to confounding effects such as neurovascular differences
- Necessary requirements for successful network detection in FMRI
  - ★Fine time resolution: usually TR = 1 second or less?
  - ★Accurate ROI selection: any missing region may result in spurious connectivity
  - ★Appropriate experiment design
  - ★Removing confounding effects

Granger Causality Analysis: `1dGC`

- `1dGC`: network detection via vector auto-regressive (VAR) modeling
  - ★ Multivariate (e.g., multiapproach instead of bivariate in BrainVoyager
  - ★ Not purely data-driven as in BrainVoyager
    - o ROIs are pre-selected by user: model-based analysis
    - o Path connectivity is statistically determined: data-driven analysis
  - ★ Written in open source language R
  - ★ Sequential mode: specifying parameters via answering questions
  - ★ Allows for time breaks in the data (e.g., inter-run intervals)
  - ★ Handles all confounding effects as covariates instead of via prior filtering
  - ★ Providing network evolution through lags
  - ★ Diagnoses model with various tests
  - ★ Individual analysis first, then group analysis on path coefficients per lag
  - ★ More details here: **http://afni.nimh.nih.gov/sscc/gangc/VAR.html**

Granger Causality Analysis: 1dGC

- A network identified by **1dGC**
  - ★Resting state data
  - ★TR=1.2 seconds
  - ★250 time points
  - ★6 ROIs
  - ★**Red**: positive connectivity
  - ★**Blue**: negative connectivity



Granger Causality Analysis: `1dGC`

- **`1dGC`**: applicability to experiment designs
  - ★ Resting state
    - o Ideal situation: time series in entirety as input with no cut and stitch involved
    - o Physiological data are likely essential for reliable results
  - ★ Block experiments
    - o Block duration ≥ 5 seconds
    - o Cut and stitch blocks together: important when handling confounding effects such as tasks/conditions of no interest, but tricky – where to cut?
  - ★ Event-related design
    - o Rapid event-related experiment: no need to cut and stitch (not practicable), but need to regress out tasks/conditions of no interest as covariates
    - o Slow event-related experiment: applicability of GC questionable
- Caveats: no magic wand - everything is statistical (correlations)
  - ★ Can't prove true causal structures, but a necessary condition for a network
  - ★ No transitive relationship: If ***A*** Granger causes ***B***, and ***B*** Granger causes ***C***, it does not necessarily follow that ***A*** Granger causes ***C***
  - ★ Missing ROIs in the model or coarse time resolution may give spurious paths
  - ★ Absence of connectivity from the analysis doesn't necessarily mean no causal relationship because model is as good as its assumptions (e.g., linearity)

Path Analysis: 1dSEM

- Path analysis (a.k.a. structural equation modeling)
  - ⋆ Start with a few pre-selected regions
  - ⋆ Assess the network based on pair-wise correlation among ROI's at group level
  - ⋆ Minimize discrepancy between covariances based on data and predicted from model
- 1dSEM: 2 modes
  - ⋆ Model validation: "confirm" a network based on data
    - o Input: network connectivity, covariance matrix, residual variance, DF
    - o H_0: we have a good model. Decision: accept, reject, or modify the model?
    - o Output: path coefficients, various fit indices, and decision on H_0
  - ⋆ Model search: look for a "best" network the data could support
    - o Start with a minimum model (flag desired paths with 1): can be empty
    - o Some paths can be excluded (0), and some optional (2)
    - o Model grows (like grass or tree branches) by adding one extra path a time
    - o "Best" in terms of various fit criteria

Correlation Analysis

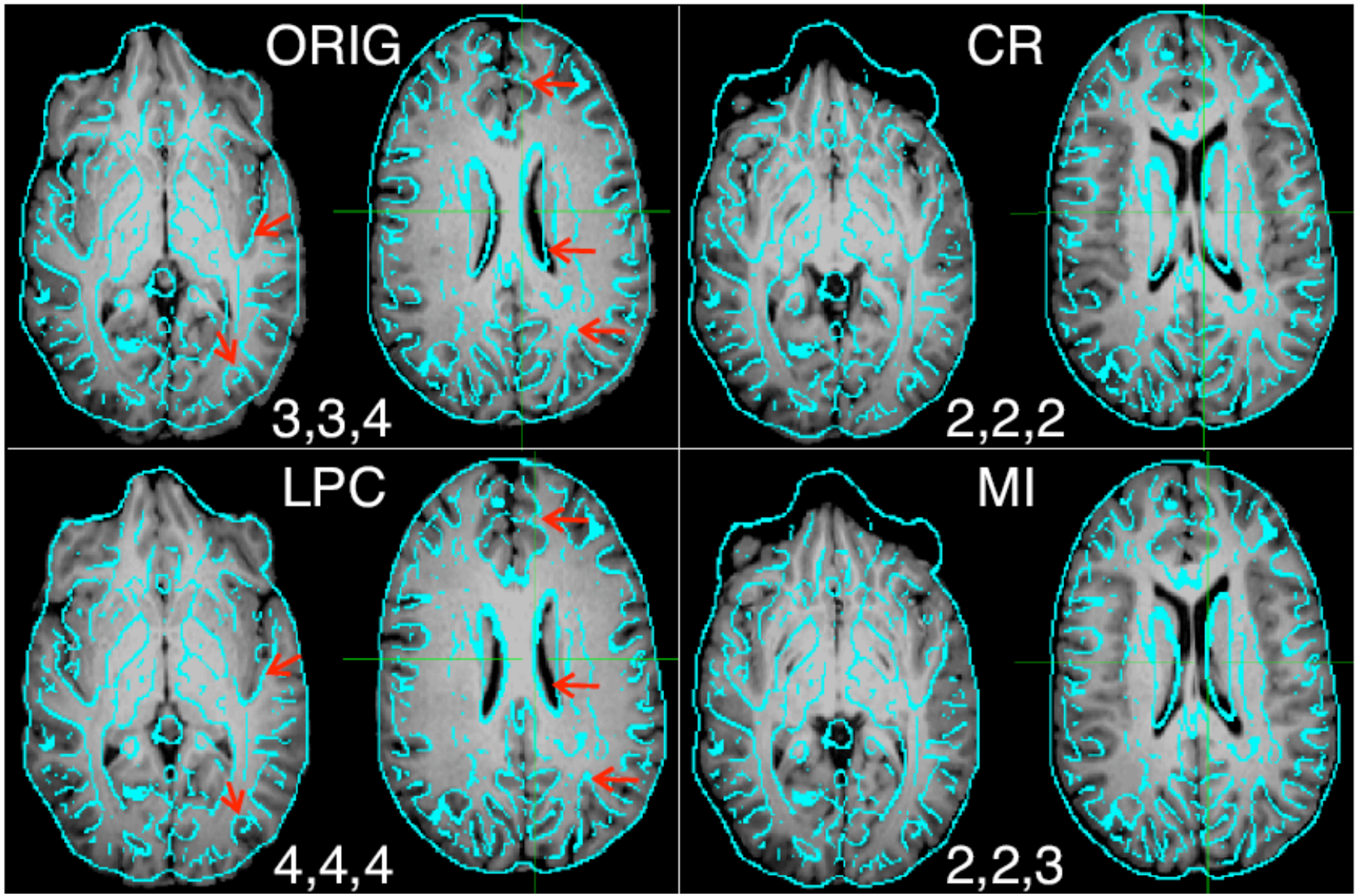
- Correlation analysis (a.k.a. functional connectivity)
  - ★ Purely data-driven
  - ★ Look for response similarity between a seed region and the rest of the brain
  - ★ No indication about directionality/causality
  - ★ Correlation between two regions doesn't necessarily mean connectivity/causality
  - ★ Confounding effects should be included as covariates
- Two kinds of correlation analysis
  - ★ Simple correlation
    - o Typically used for resting state experiments
    - o Details: **http://afni.nimh.nih.gov/sscc/gangc/SimCorrAna.html**
  - ★ Context-dependent correlation (a.k.a. **PPI**)
    - o Look for correlation under the context of a task/condition
    - o Effect of the seed region on a target depends on the specific task/condition or the interaction between the task/condition (psycho-) and the neuronal response (physiological) of the seed
    - o Steps: **http://afni.nimh.nih.gov/sscc/gangc/CD-CorrAna.html**

align_epi_anat

Aligning EPI and T1-weighted structural volumes

Alignment of EPI and Anatomical Datasets

- New LPC method gives consistently better alignment—based on visual inspection—over other cost functionals, including MI and CR



align_epi_anat.py

- aligns EPI and structural datasets using LPC method in **3dAllineate**
- **align_epi_anat.py** script prepares data, then does the work:
  - deobliquing
  - skull stripping
  - slice timing correction
  - motion correction
  - weighting, resampling
  - Talaraich transformation
- Applies concatenated matrices (oblique, volume registration, tlrc)
- Aligns EPI→Anat **or** Anat→EPI

Basic Example:

```
# align anatomical dataset to epi dataset at sub-brick 5
align_epi_anat.py -anat anat+orig -epi epi+orig \
      -epi_base 5
```

align_epi_anat.py

More advanced example:

Transform EPI dataset to match Anat

Register "child EPI" datasets to "parent" EPI and align with Anat

Warp EPI and child EPI datasets to +tlrc space based on existing

Anatomical +tlrc datase

Also, create composite edge images

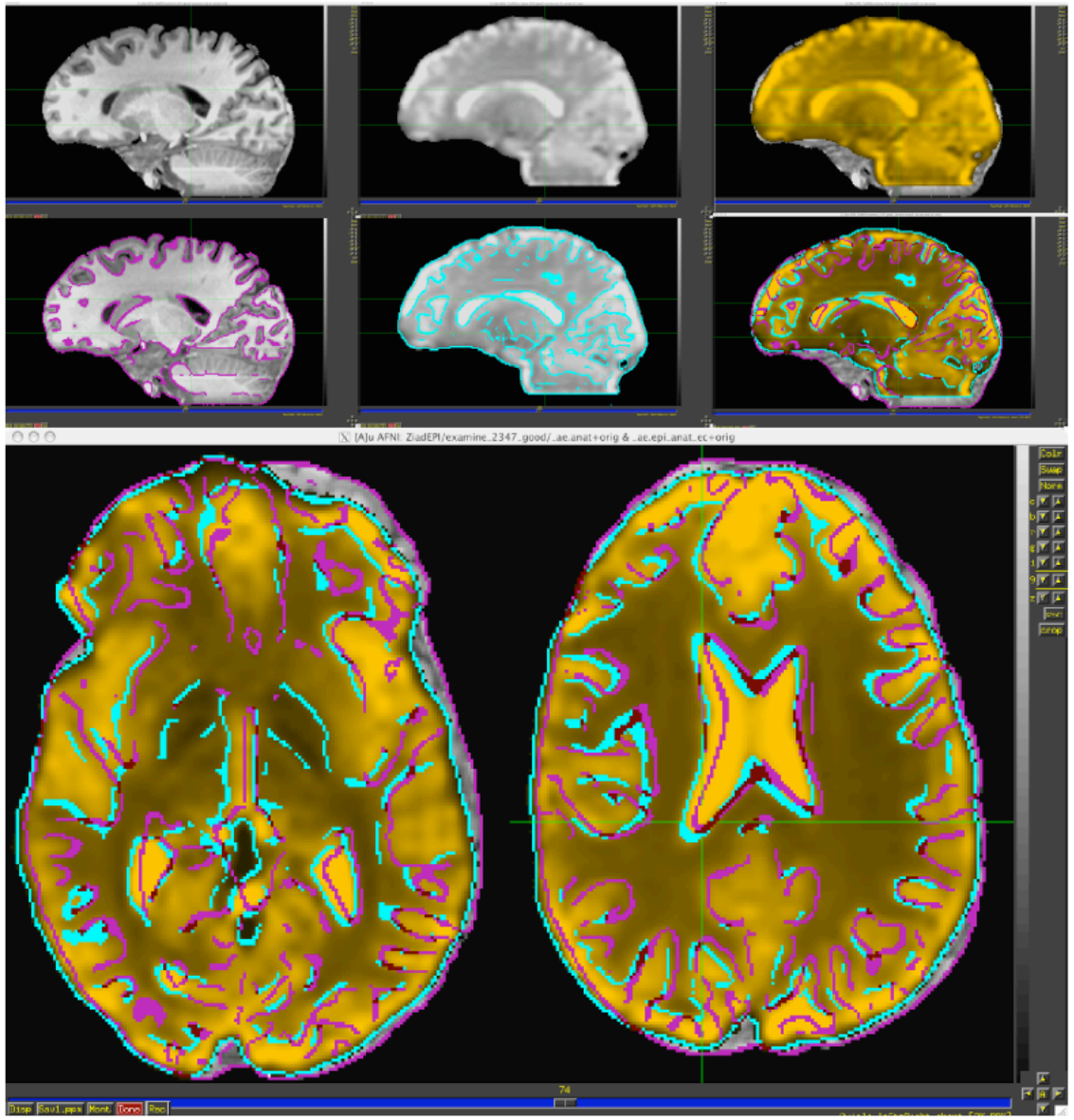
```
@auto_tlrc -base ~/abin/TT_N27+tlrc \
   -input sb23_mpra+orig
align_epi_anat.py -anat sb23_mpra+orig                \
        -epi epi_r03+orig                             \
         -epi_base 6 -child_epi epi_r??+orig.HEAD     \
         -epi2anat -suffix _al2anat                   \
         -tlrc_apar sb23_mpra_at+tlrc -AddEdge
```

Flexibility in options for cost functionals and processing steps allow alternate uses. Already used also for T_1-to-T_1 (SPGR, FLAIR, 3T, 7T), EPI-to-EPI, rat and monkey data, and partial coverage data.

Assessment of Alignment

- AFNI provides multiple viewers, overlay/underlay switching, opacity control
- Edge-enhanced display now available with dual edge composite or single edge options with **`@AddEdge`** and **`-AddEdge`** option to **`align_epi_anat.py`**
- **`@AddEdge`** script drives AFNI GUI to display pre-aligned and post-aligned datasets

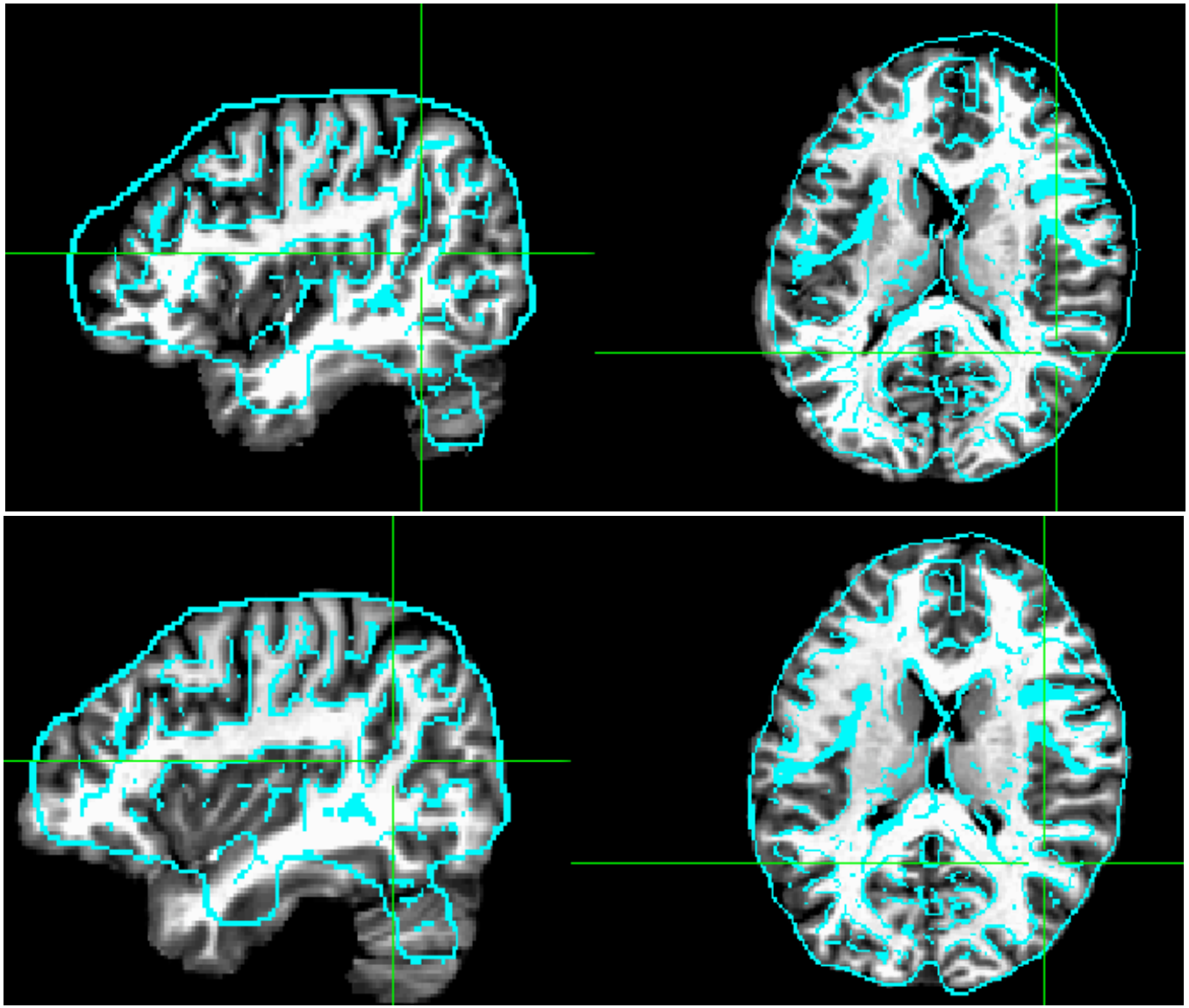
A new method for improving functional-to-structural MRI alignment using local Pearson correlation, *NeuroImage*, in press (now online)



`align_epi_anat.py` example output

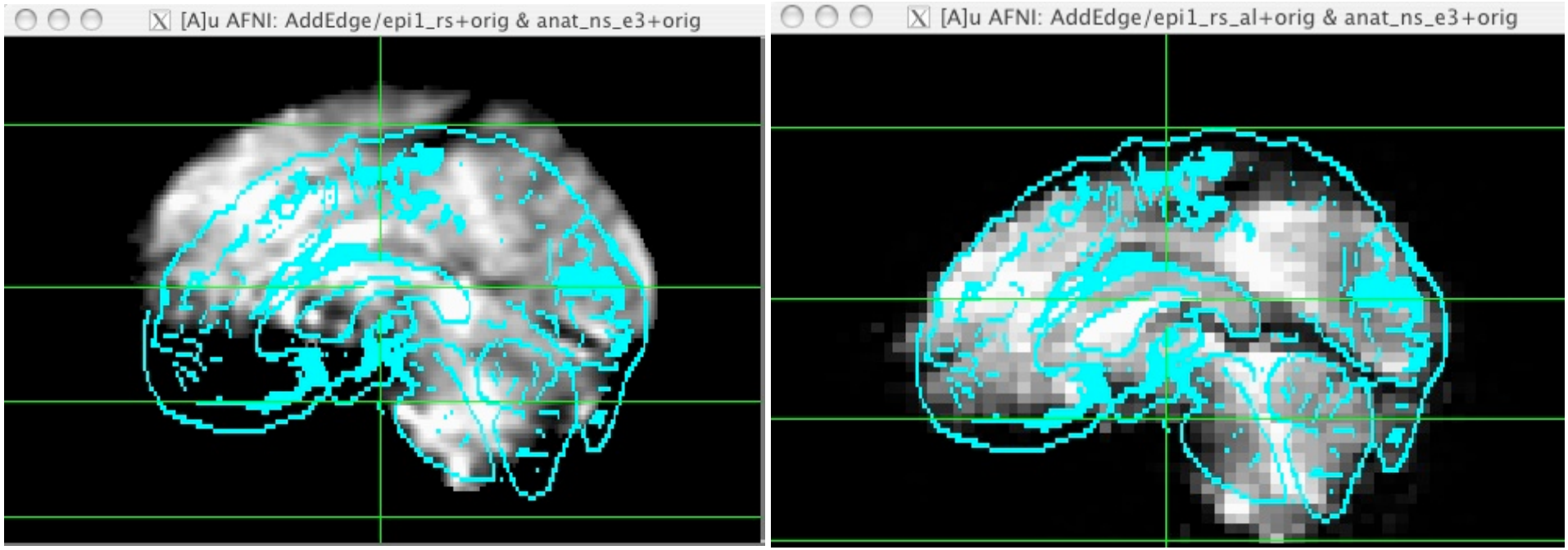
Pre-alignment

Post-alignment



`@AddEdge -single-edge` display shows before and after with edges from transformed EPI dataset as overlay

align_epi_anat.py example output



Pre-alignment

Post-alignment

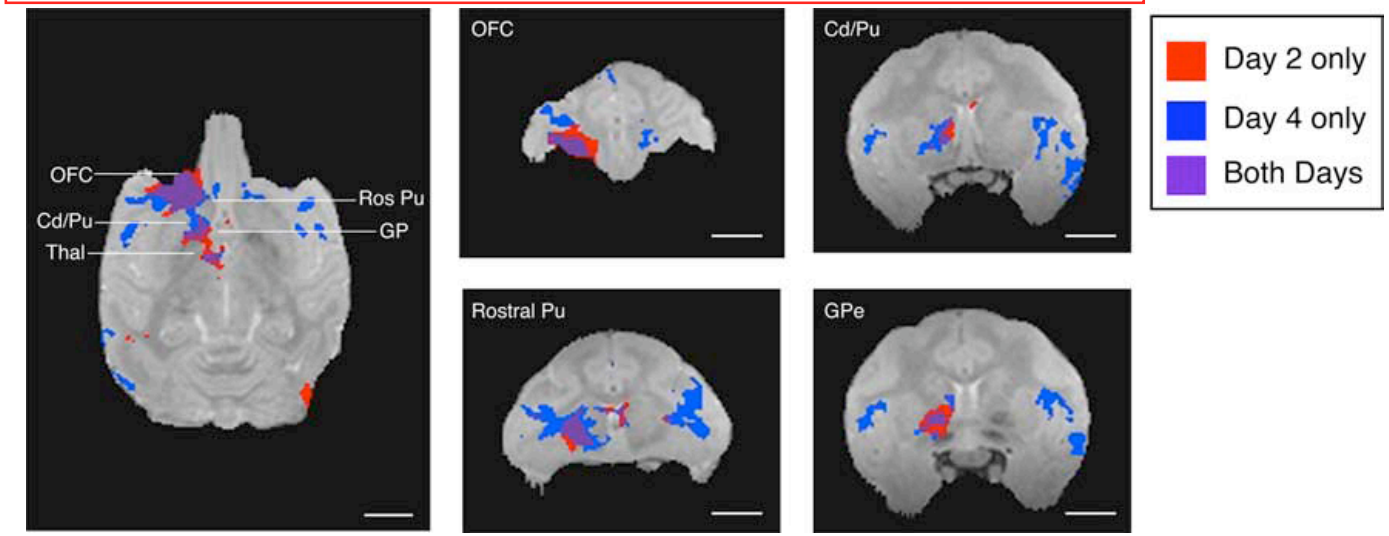
Example data from message board posting.
@AddEdge -single-edge display shows before and after with transformed EPI dataset in the underlay and the anatomical edge in the overlay

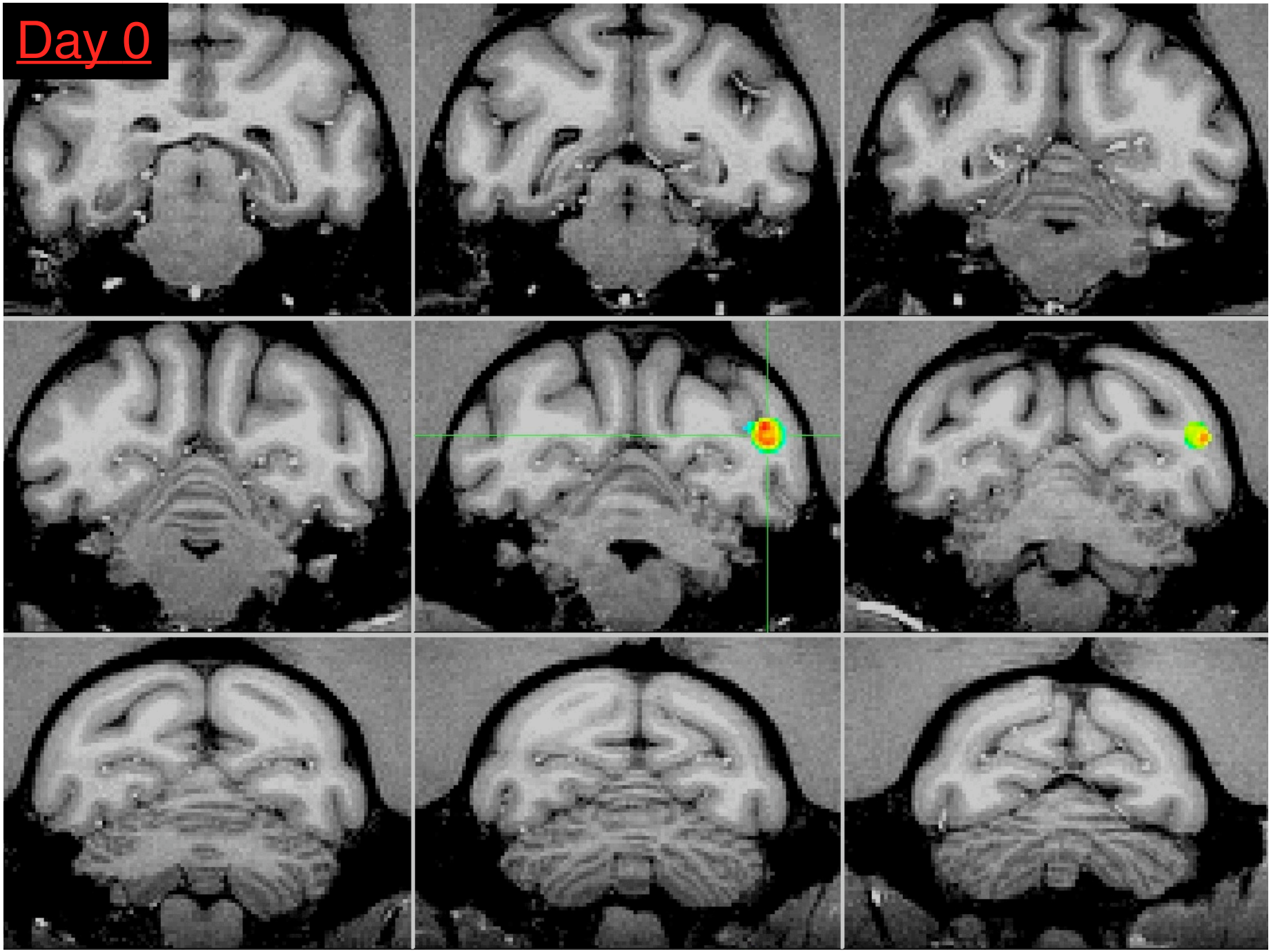
Manganese Enhanced MRI

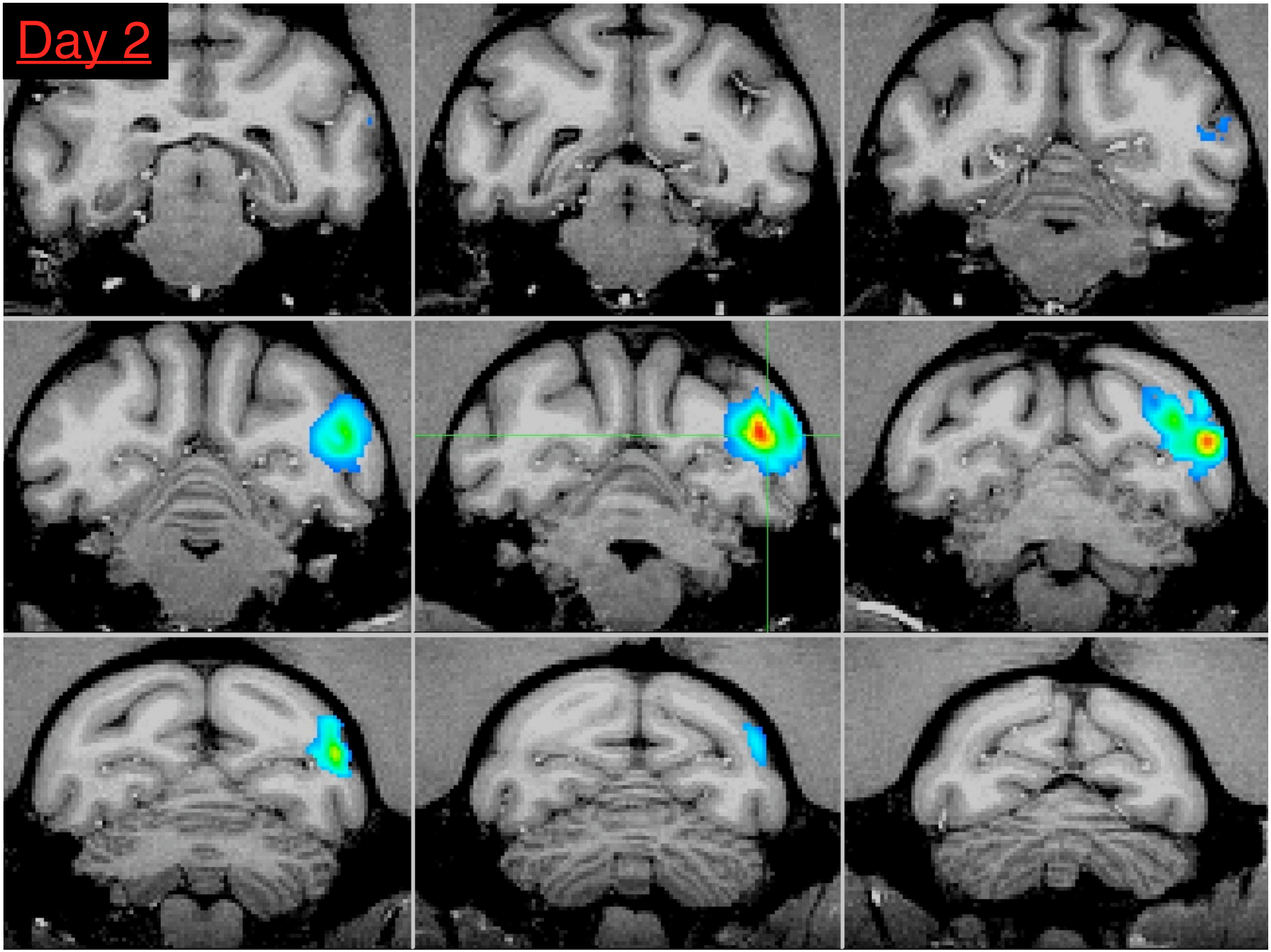
Manganese Enhanced MRI

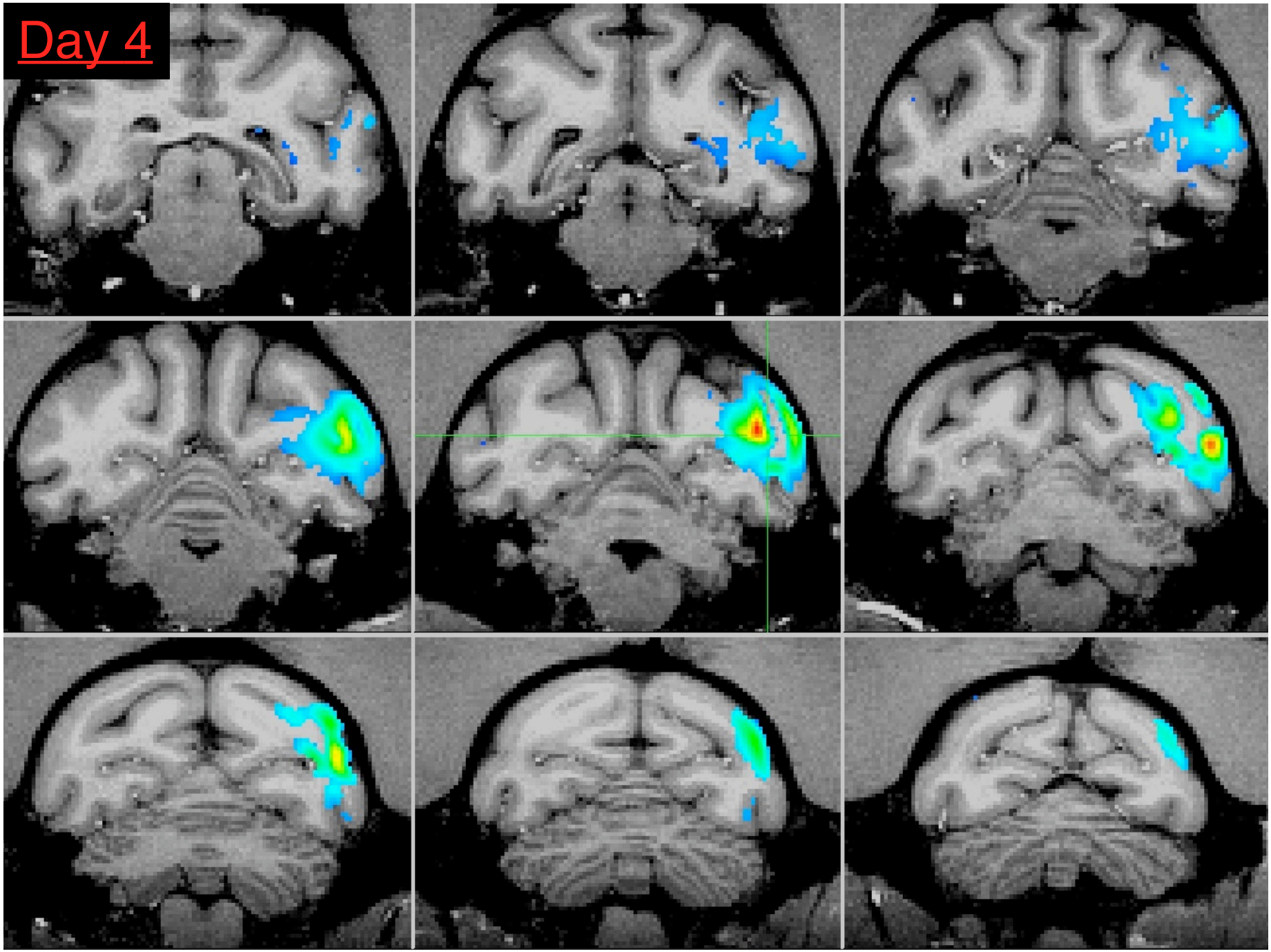
- We have a pipeline for *voxelwise* detection of Manganese induced signal enhancement
  - ★ Robust skull removal and intra-subject longitudinal alignment
  - ★ Parametric and non-parametric signal detection approaches with multiple comparison correction
  - ★ Output of summary results from each stage for quality checking
  - ★ Morals from our experiences thus far:
    - o Get as many scans as possible (10+) in pre-injection phase
    - o Get several post-injection scans at each time point of interest (2+)
    - o Examine your images immediately for bad artifacts and correct***!!***

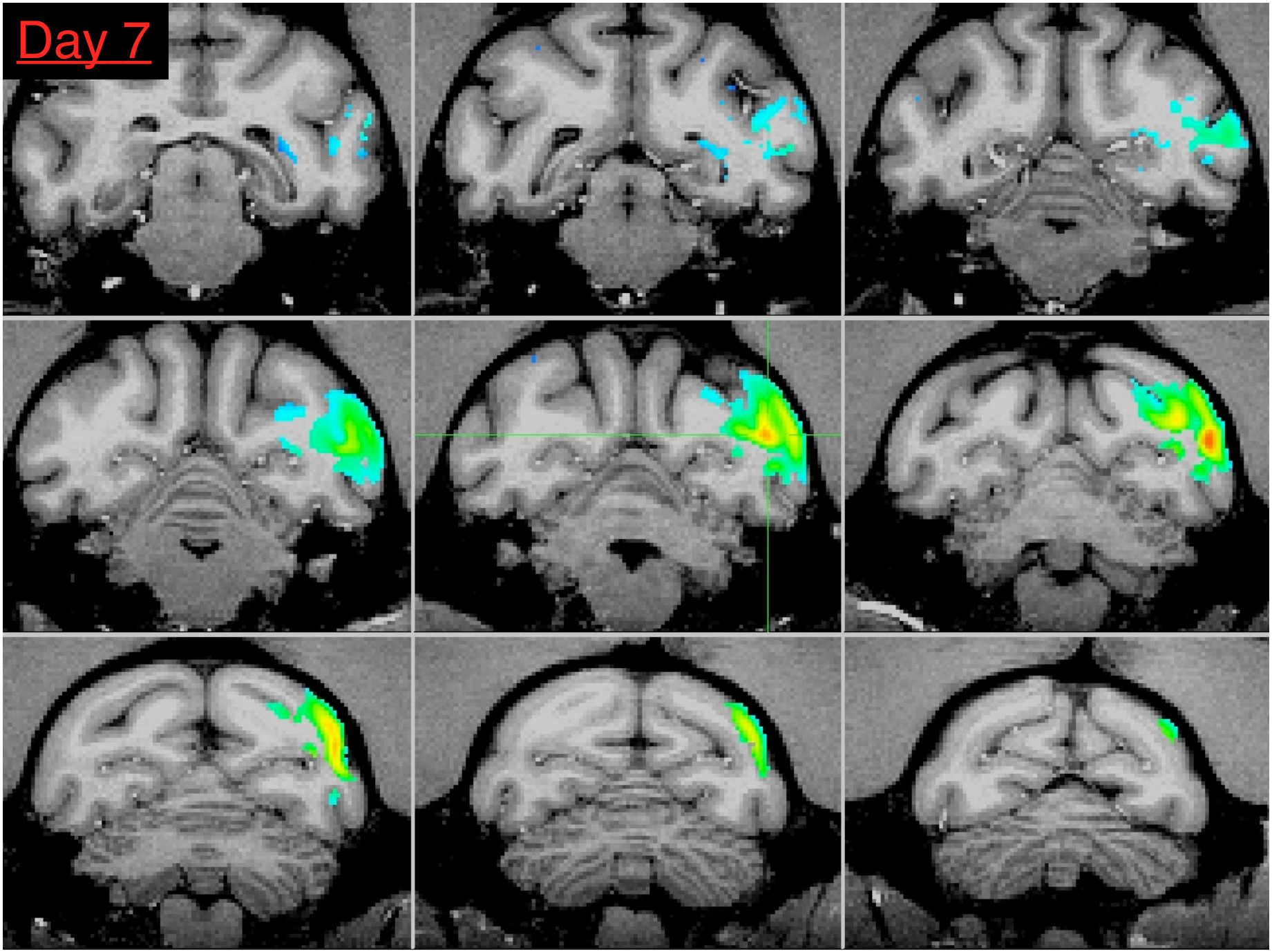
First generation results: Fig. 7, Simmons et al. J. Neuroscience 08




Day 0


Day 2


Day 4


Day 7

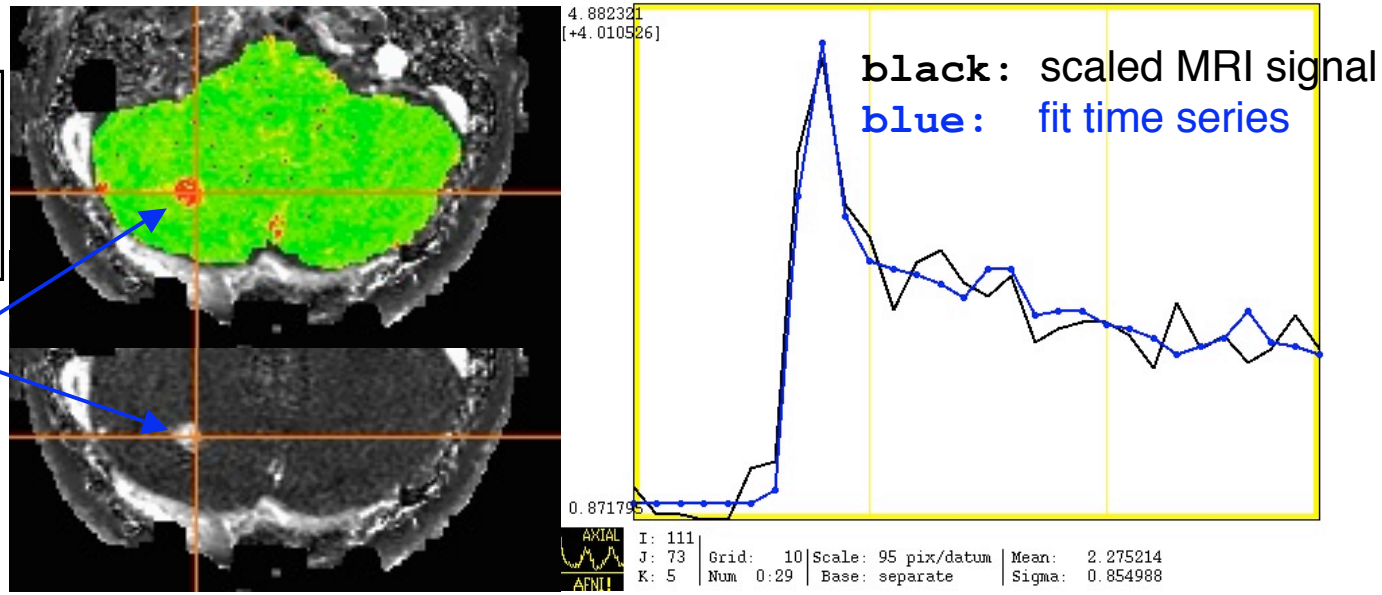
DCEMRI

Dynamic Contrast Enhanced MRI: Analysis with `3dNLfim`

DEMRI: Dynamic (contrast) Enhanced MRI

Ve (extracellular, extravascular volume) estimate overlayed on MRI time series

tumor location



- Collaboration with John Butman, Hemant Sarin in Clinical Center, on Dynamic Contrast Enhanced MRI (DCEMRI or DEMRI)
- Gd-DTPA injection – large, relatively inert molecule that doesn't pass intact blood-brain barrier injected after short baseline, but brightens T1-weighted images
- Non-linear model in **`3dNLfim`** framework to compute kinetic parameters (Ktrans, kep, Ve, fpv) of brain tissue in a two compartment model to model breakdown of blood-brain barrier
- This implementation in AFNI is the only freely available DEMRI software for volumetric analysis (at this time)

Realtime AFNI at NIH Scanners

Realtime FMRI-Feedback at NIH Scanners

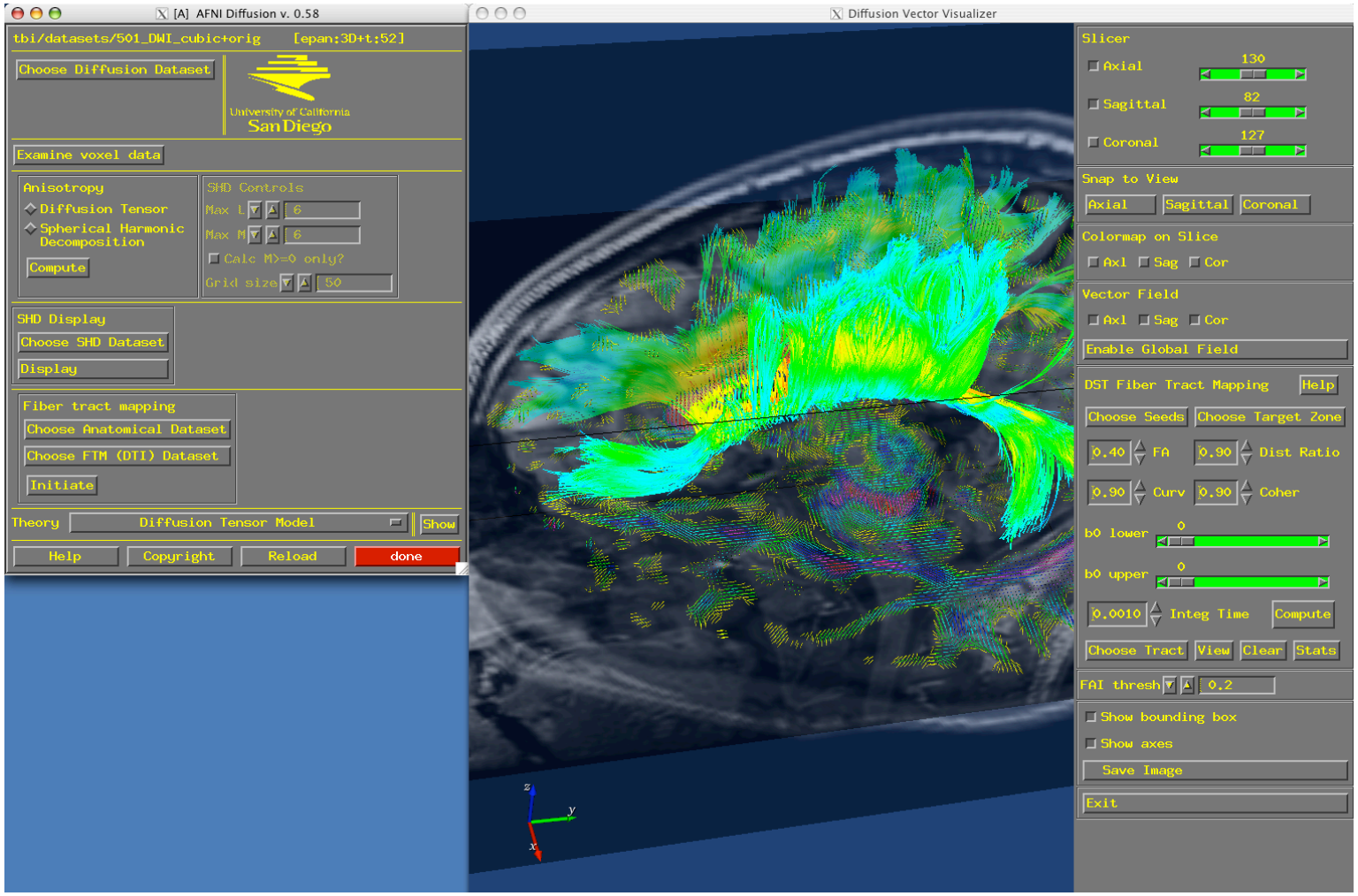
- Enhanced version of the NIH realtime MRI scanner software
  - ★ installed on all GE MRI scanners (written by Jerzy Bodurka)
  - ★ can be used with AFNI to conduct realtime FMRI with feedback to the subject
  - ★ a sample real-time plotting tool is installed on all FMRIF MRI scanners
    - o based on **`serial_helper`**, with updates written by Javier and Jerzy
    - o uses **`Grace`**: a 2D plotting tool for the X Window System
- MRI data is captured each TR and used to drive the realtime subject feedback display
  - ★ motion parameters: to show the subject when they move “too much”
  - ★ ROI averages: to show real-time “activation” at one or more ROIs
  - ★ raw (registered) voxel data: for other nefarious purposes
- AFNI’s realtime updates:
  - ★ **`Dimon`** → **`afni`** is more responsive, to improve subject feedback
  - ★ has enhanced stability and environmental controls
  - ★ **`afni`** can send ROI averages or raw voxel data to **`serial_helper`**, each TR

Diffusion Tensor Imaging

New Plugin from UCSD

Diffusion Plug-in

- From UCSD group led by Larry Frank with Greg Balls, Ning Kang
- seed-based “diffusion model” tractography allows for fiber crossing
- Pretty 3D primary eigenvector and FA-encoded tractography display
- Coming real-soon-now …

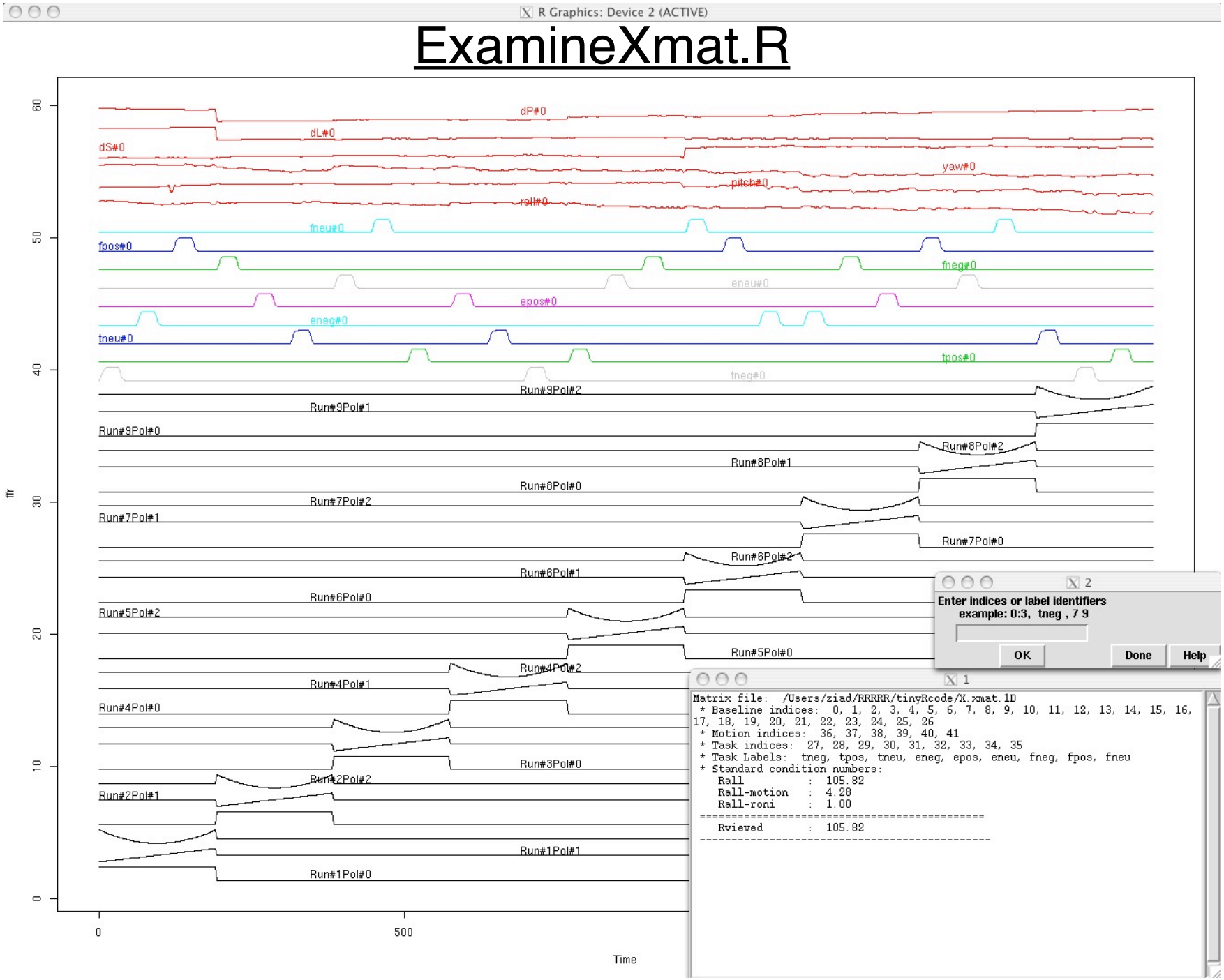


ExamineXmat

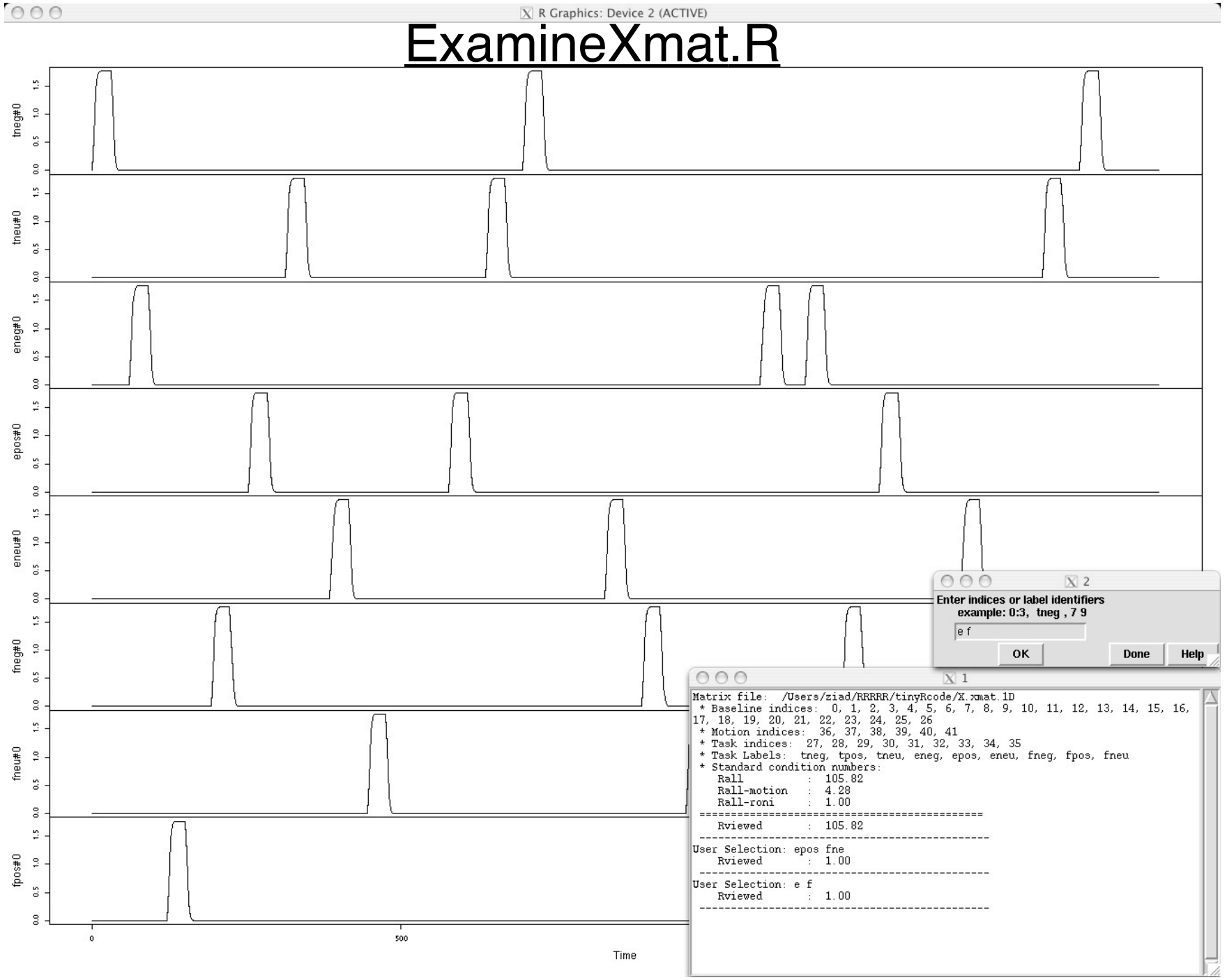
Putting your time series regression matrix up on the rack and checking it for problems

- A tool to examine design matrices
  - Visualize matrix and selected subsets of it
  - Condition numbers for various subsets of matrix and selected regressors

ExamineXmat.R



ExamineXmat.R




"That's
all
folks!"