Functional MRI Analysis with AFNI accents

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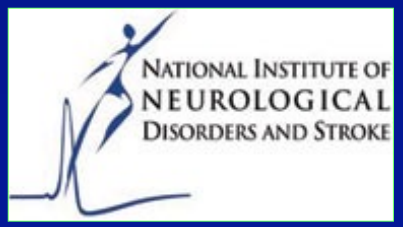

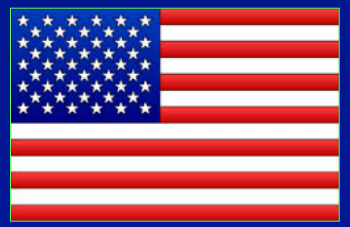

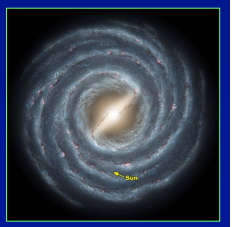

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To Dream the Impossible Dream

- *i.e.*, To explain FMRI Analysis in 60 min

- Basis for FMRI time series analysis:
  - 10-20 inter-twined concepts
  - pre-processing ; individual subject analysis ; group analysis ; connectivity ; …

- Many seem simple, but ***each*** one has subtleties and points of contention

- Can only cover the most central ideas now
  - **Absolute Beginners**: Confusion Ahead*!*

Some Goals of FMRI Analyses

- **Task-based experiments**
  - **Per subject:** estimate amplitude of BOLD response to each different type of stimulus
  - Model **+** Estimate inter-regional correlations between fluctuations in BOLD responses
- **Resting-state experiments**
  - Measure spatial patterns in coherent fluctuations in spontaneous BOLD effects
- **Group level**
  - Combine and contrast per subject results

Conceptual Basis - 1

- **Time shifting** = pretend get 3D snapshot
- **Despiking** = remove large blips
- **Image Registration** (AKA alignment)
  - intra-EPI time series, and EPI-Structural
- **Blurring in space** = lower resolution :-(*&* less noise :-) *&* more group overlap :-)
- **Masking** = ignore non-brain voxels
- **Scaling** = normalizing data amplitude
  - Makes inter-subject comparisons more valid

Conceptual Basis - 2

- **Time series regression**
  - model of the BOLD response in the data = **H**emodynamic **R**esponse **F**unction **convolved with** stimulus timing
  - plus baseline (null hypothesis) model
  - plus physiological noise
  - plus allow for serial correlation
  - plus allow for random response strength (!!)
- **Talairach-ing =** Spatial Normalization
  - Talairach, MNI-152, …
  - affine and nonlinear spatial transformations

Conceptual Basis - 3

- **Group Analyses** = Putting it all together

- – **ANOVA**, **LME**, **MVM**, Meta-Analyses, …
- **Blobs** = Spatial models of activation

- – Assigning statistical significance to blobs
- **Connectivity** = Inter-regional analyses
  - – **SEM**, **PPI**, **SVAR**, **DCM**, …

  - – Resting state FMRI (Connectome!)
- **Dimensional factorization**
  - – Components, such as PCA, ICA

Conceptual Basis - 4

- **Data Formats** = NIfTI-1.x is your friend
- **Software** for FMRI analyses:
  - **AFNI***, **BrainVoyager**, **FSL***, **SPM***, **…**
  - Whichever you use, **don't blindly assume** the software works perfectly all the time

*open-source

- Most important thing I will say today

Understand and check the steps applied to your data!

- 2nd most important: **Is no "best" way to analyze data, just "reasonable"** ***ways***

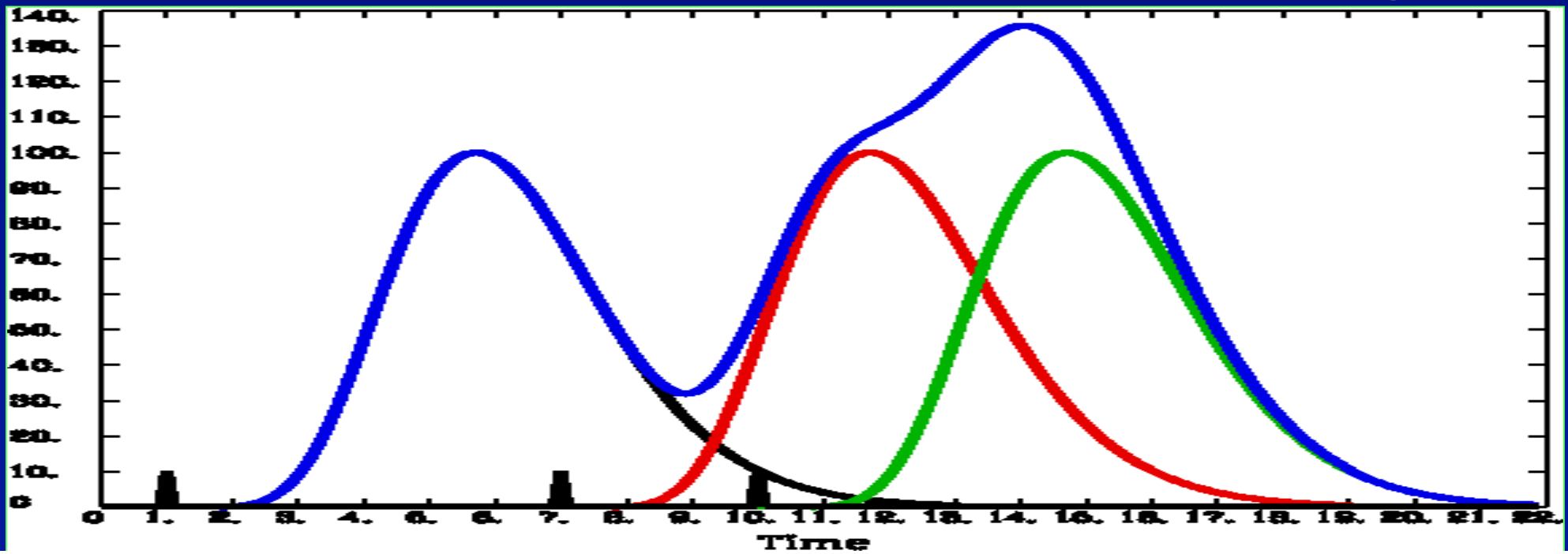
Time Series Regression

- After pre-processing the images:
  - Each voxel time series is (separately) fit to an idealized model of the BOLD effect
  - Plus other (nuisance) components
    - Baseline drift, physiological artifacts, …

- Estimated parameters of the BOLD model are the "**activation map**"
  - Amplitude of response = most common
  - Shape of response can also be modeled
  - Statistics on parameters allow thresholding

Basic BOLD Model

- Assumptions:
  - BOLD response starts ≈ 2s after "activity"
  - Rises to peak about ≈ 4s later
  - Drops to baseline about ≈ 5s post-activity
  - Overlapping (in time) BOLD responses from separate events add up **= linearity**



Further Model Pieces-Parts

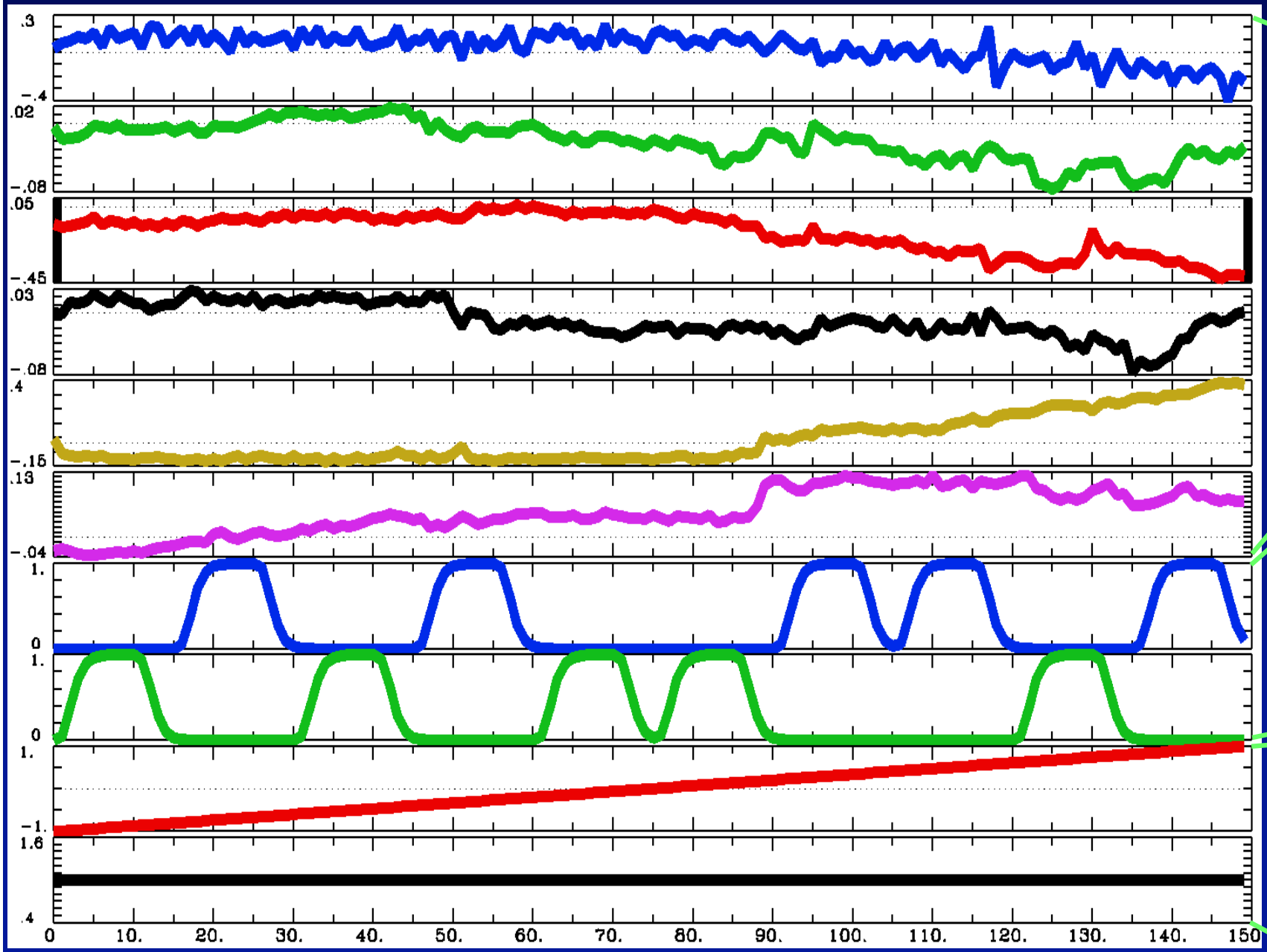
- FMRI data = pretty noisy ➔
  - Need multiple copies of each stimulus type
  - Assume BOLD responses same within type

- Slow drifting terms in baseline *highpass filter*
- Residual effects of subject movements
  - Use motion parameters as extra regressors

- Include physiological regressors (**RetroICOR**)
  - From monitoring heartbeat *&* respiration

- Serial correlation in noise ➔ use **GLSQ**

Sample Linear Regression Model



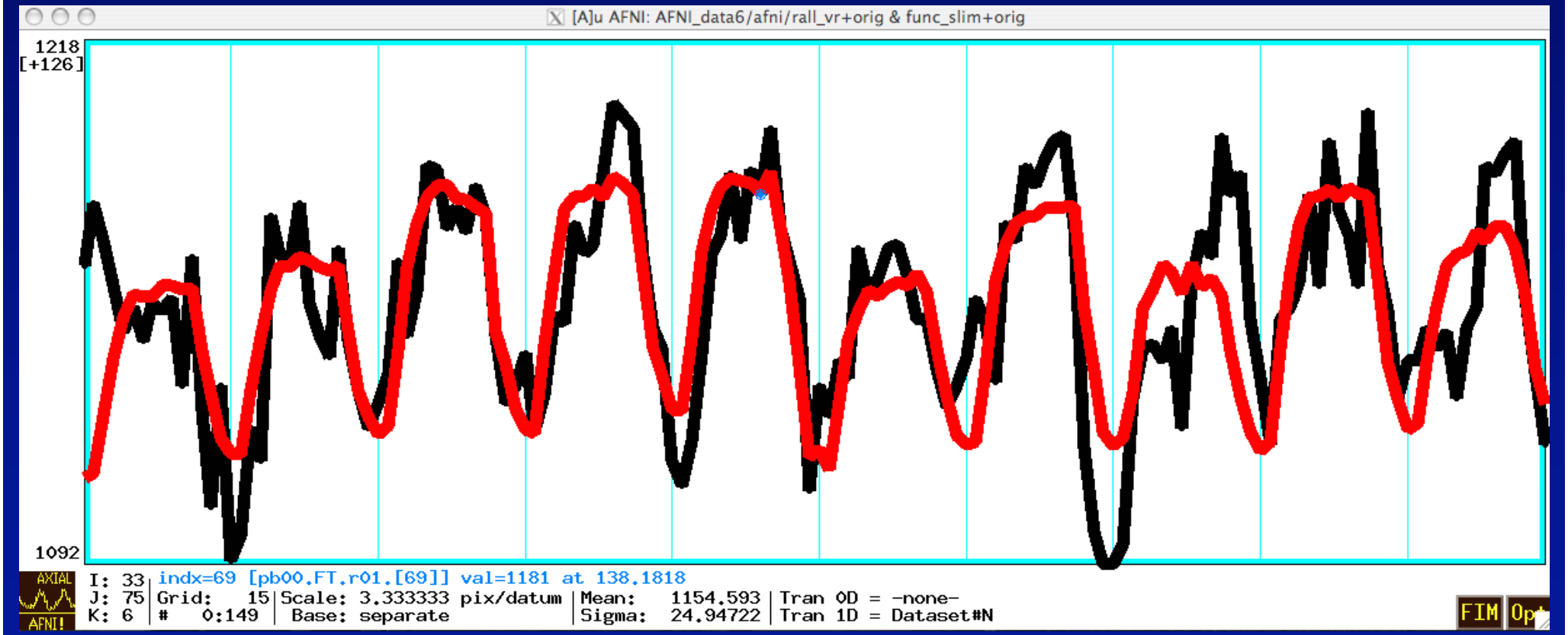
Motion Params

BOLD + Stimuli Models

Slow Drift Model

One Voxel's Time Series

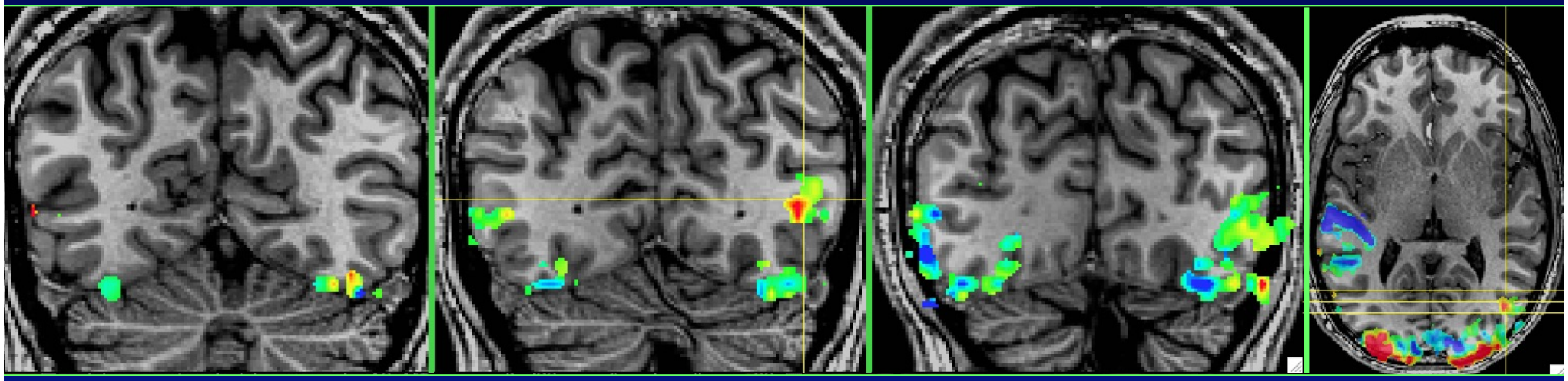
- This is good data at a high signal voxel
- 2 stimulus classes; 1 block every 30s; TR=2s



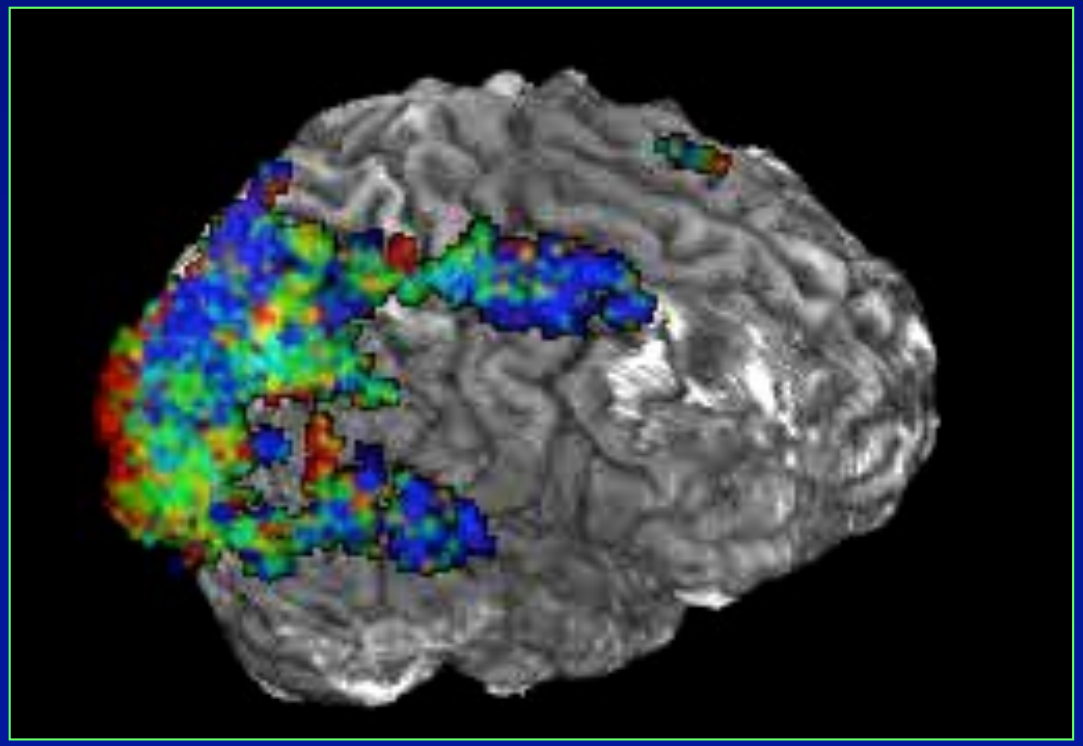
Black = 150 data points **Red** = fitted model (BOLD++)

Data: Mike Beauchamp/UTexas

Results from One Subject



ShowThru rendering of difference between visual and auditory BOLD amplitudes



Talairach-ing (AKA Normalizing)

- For combining and contrasting results across groups of subjects

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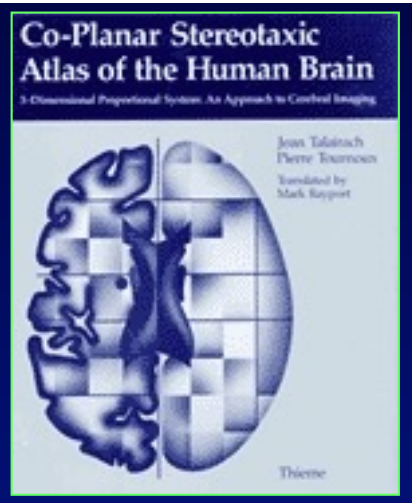
- Align 3D brain images (usually structural volumes) to a common template
  - Assumption: function follows structure

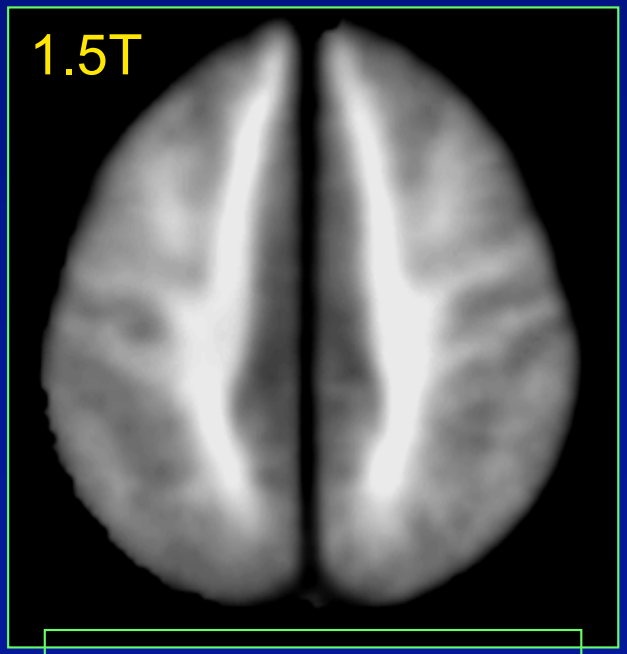
- Then merge results on a voxel-wise basis on this new grid
  - Accuracy of alignment = 5-10 mm
  - Spatial blurring = more inter-subject overlap

Templates

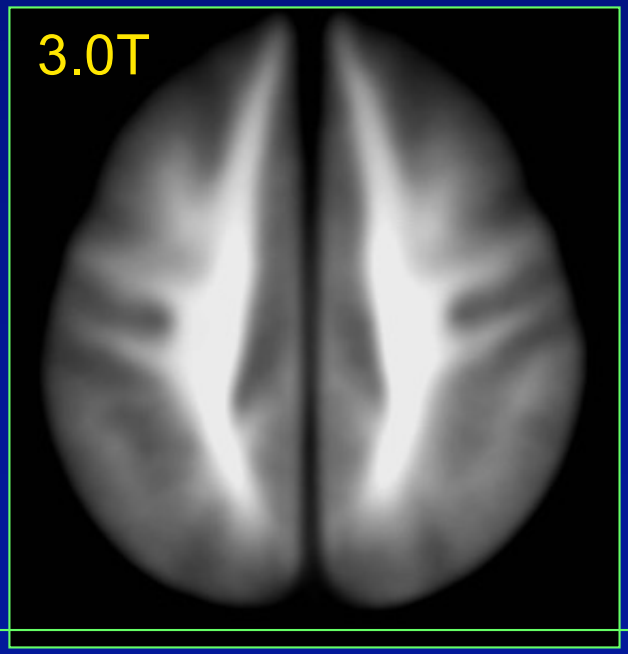


- Ye Good Olde Days = Talairach-Tournoux atlas

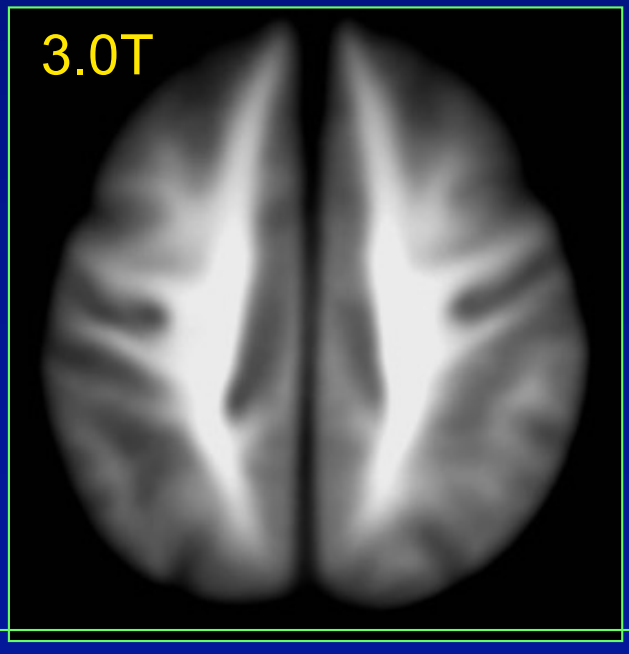
- Decadent modern times = MNI-152 template = average of 152 brain images



MNI-152 (affine)



FCON-1000 (affine)



FCON-1000 (poly9)

Custom Templates

- Can register all subjects in study together iteratively
  - Then average to get a study-specific template
  - Can use high order nonlinear spatial warps for better structural feature alignment ⇒

101 subjects
AFNI *3dQwarp*

Data: MindBoggle

- Alternatives:
  - ROI or Atlas-based analyses
  - Cortical surface-based analyses [*cf.* **SUMA**]

Group Analysis

- Group analysis is done in 2 stages:
  - Individual subject analyses reduce EPI time series to BOLD response parameters
  - Inter-subject analysis is done on these parameters (*e.g.*, measures of amplitude)
  - Usually have some estimate of reliability of these parameters (*e.g.*, standard deviation)

- Normalization of data magnitude and spatial normalization are important steps

Flavors of Group Analysis - 1

- *t*-tests for simple 2-way contrasts

- **ANOVA** of various complexities for more intricate collective effects
  - Usually end up wanting to do *t*-tests on these "main" effects to see **What's Up** (*Doc*)
  - Plain **ANOVA** relies on many assumptions about distribution of randomness
    - Independent noise (or all samples are correlated the same way; "sphericity") ; Gaussianity ; Homoscedasticity (all samples have same variance) ; Balanced designs

Flavors of Group Analysis - 2

- Linear Mixed Effects (**LME**) and Multi-Variate Models (**MVM**) generalize **ANOVA** to avoid such assumptions

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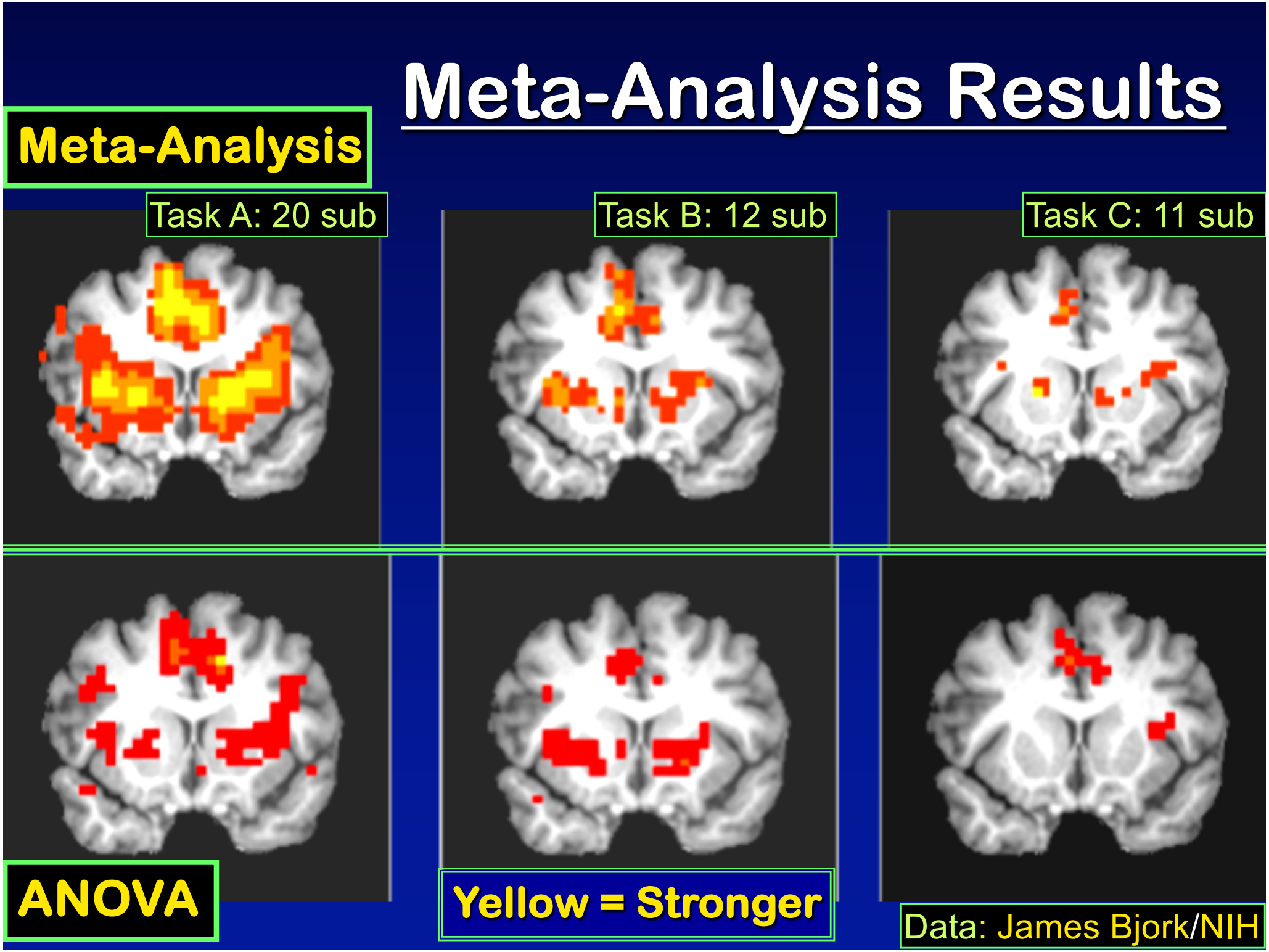
- Meta-Analysis: Statistics run on statistics
  - Which is exactly what we are doing in FMRI
  - Many developments in the 1990s
  - Can be applied to FMRI data, using not just the individual subject amplitudes, but also their reliability estimates; *cf*. **AFNI** and **FSL**
  - Can also model non-Gaussianity (outliers)

Meta-Analysis Results



✪Blobs! [AKA Clusters]

- For most purposes, if we saw that all the *statistically* significant activation was just in tiny and scattered clusters, we would be suspicious and upset

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- We not only threshold on voxel-wise ***t***- or ***F***-statistics, but we also threshold on size of contiguous supra-threshold clusters

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- Allows us to lower the per-voxel threshold by raising the cluster-size threshold to maintain error rate control

Blob Significance (!!)

- Probability that a smooth ***noise-only*** image would produce a blob, with each voxel above a given threshold and the size of the blob above a given cutoff

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- Cannot be calculated in closed form :-(

- Two approaches available:
  - Asymptotic formula for high per-voxel thresholds and high degrees of smoothness — *K Worsley*
  - Direct Monte-Carlo simulation (brute force) — **AFNI**
  - Which to use? Depends on your software!

✪Connectivity

- **FMRI basis**: Fluctuations in neural activity ➔ fluctuations in BOLD signal

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- ➔Task performance changes between repetitions can give coherent signal changes in remote brain regions

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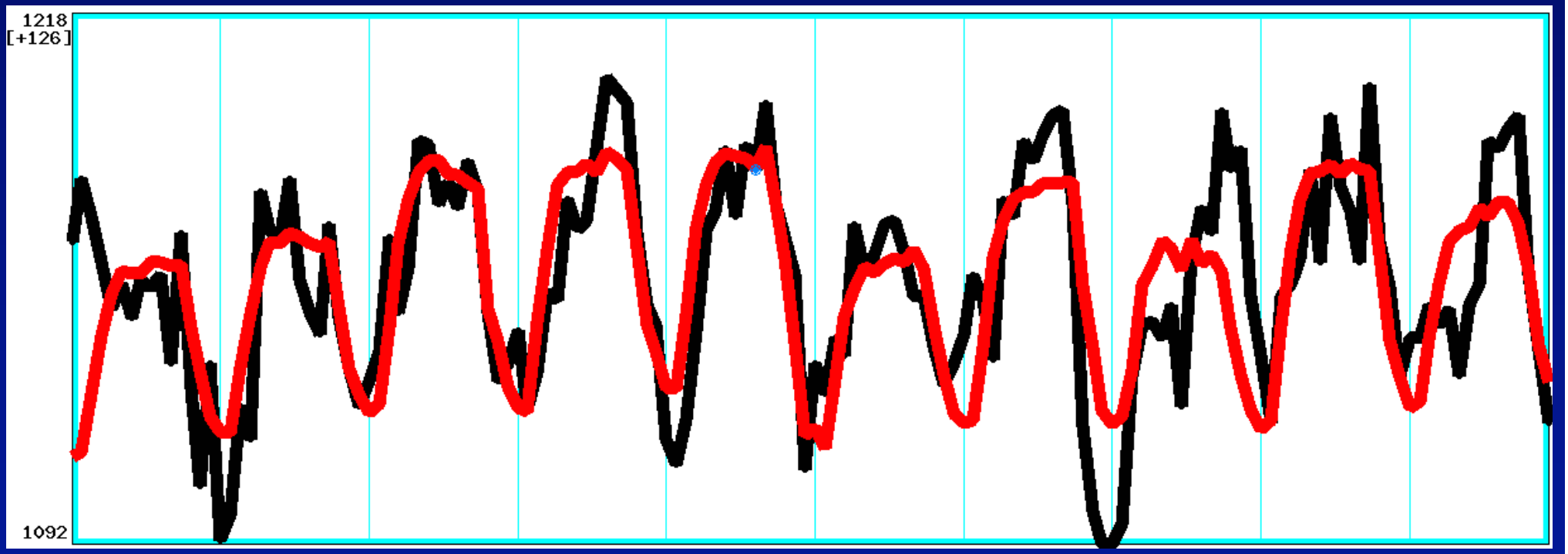
- Can look for ***causal*** changes also:
  - *e.g.*, Predictability of one region's data from another's data at a ***previous*** time step
  - Limited TR of FMRI data makes this iffy
    - Probably need TR **<** 1s to do this well

Task-Based Connectivity

- Fluctuations from model fit can be bigger than noise; recall this graph from 1 voxel

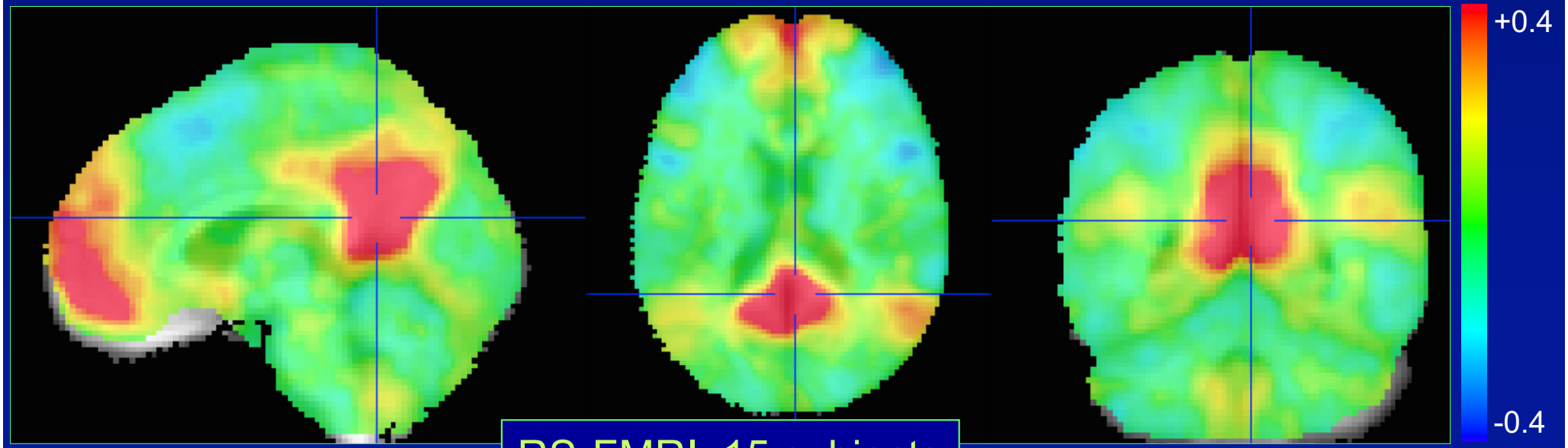


- So can subtract the fit and then look for inter-voxel correlations (if have enough data)

Flavors of Connectivity - 1

- Simple correlation from a seed region (or voxel) with all other voxels in brain
  - Ambitiously: Correlate All-with-All :-)

- Then group analysis for statistical power
- Used in resting-state FMRI analyses



RS-FMRI: 15 subjects

Data: Alex Martin/NIH

Flavors of Connectivity - 2

- PPI = **P**sycho-**P**hysiological **I**nteraction
  - We call it "Context Dependent Correlation"
  - Augment the regression model with data time series averaged from a seed region
    - And multiplied by **+1** in context **A**, **-1** in context **B**, and **0** in other cases (*e.g.*, baseline)
  - Fit parameter for new regressor measures fluctuations in EPI signal whose correlation with seed region **changes** between contexts (**A** & **B**)
  - Context = "Psycho" ; EPI/BOLD = "Physio"

Flavors of Connectivity - 3

- Network models use multiple regions, try to fit multiple dependencies amongst them
  - FMRI noise means must average over pre-chosen regions before network hunting+fitting
  - Anatomical ROIs or Functional ROIs?

- Instantaneous directional effects:
  - Structural Equation Modeling (**SEM**)

- Delayed (causal) effects:
  - Dynamic Causal Modeling (**DCM**)
  - Structural Vector AutoRegression (**SVAR**)

Connectivity Conclusions

- Often: make statement about ***changes*** in connectivity between two situations
  - Absolute connectivity statements are somewhat less common (though not rare)

- When contrasting subject groups, must be careful that physiological differences (*e.g.*, respiration) are accounted for
  - Especially in resting-state studies, which don't have any task-timing to which we can tie down the analysis

Final Gratuitous Remarks

- Multi-stimulus linear regression models for task-based FMRI appear in mid-1990s

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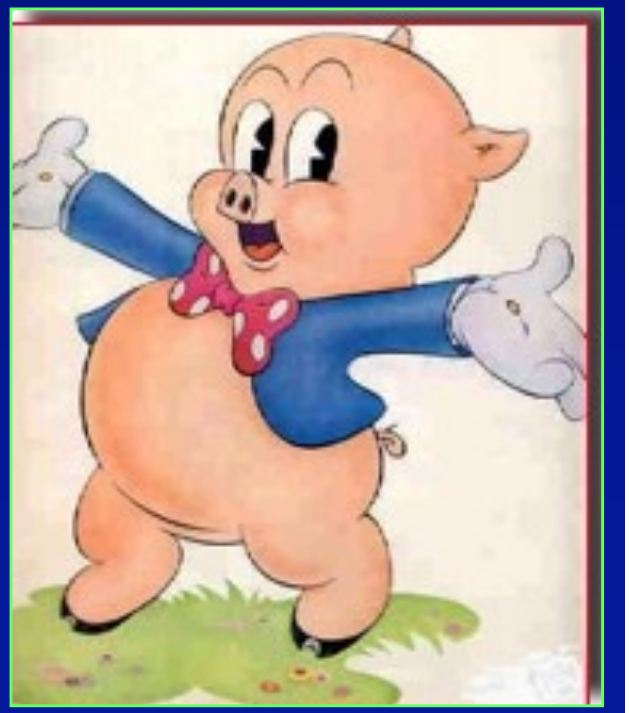
- Since then, most task-based FMRI time series analysis improvements have been incremental and/or controversial and/or of limited scope — **IMHO**

- Are we near the limit of what kind of information can be gleaned from current-technology FMRI datasets?
  - **Or do we just need to be cleverer?**

Th'Th'That's All Folks!

- Thanks must go to
  - **Ziad Saad, Gang Chen, Rick Reynolds, Daniel Glen, Paul Taylor**
  - **James Hyde**, Peter Bandettini, Andrzej Jesmanowicz
  - Elliot Stein, Jeff Binder, Steve Rao, Alex Martin, Leslie Ungerleider, Ted Deyoe, … and too many more brain-ologists to name herein



Data: Warner Bros.