# LECTURE 10: MODELING THE FMRI DATA AT THE FIRST LEVEL

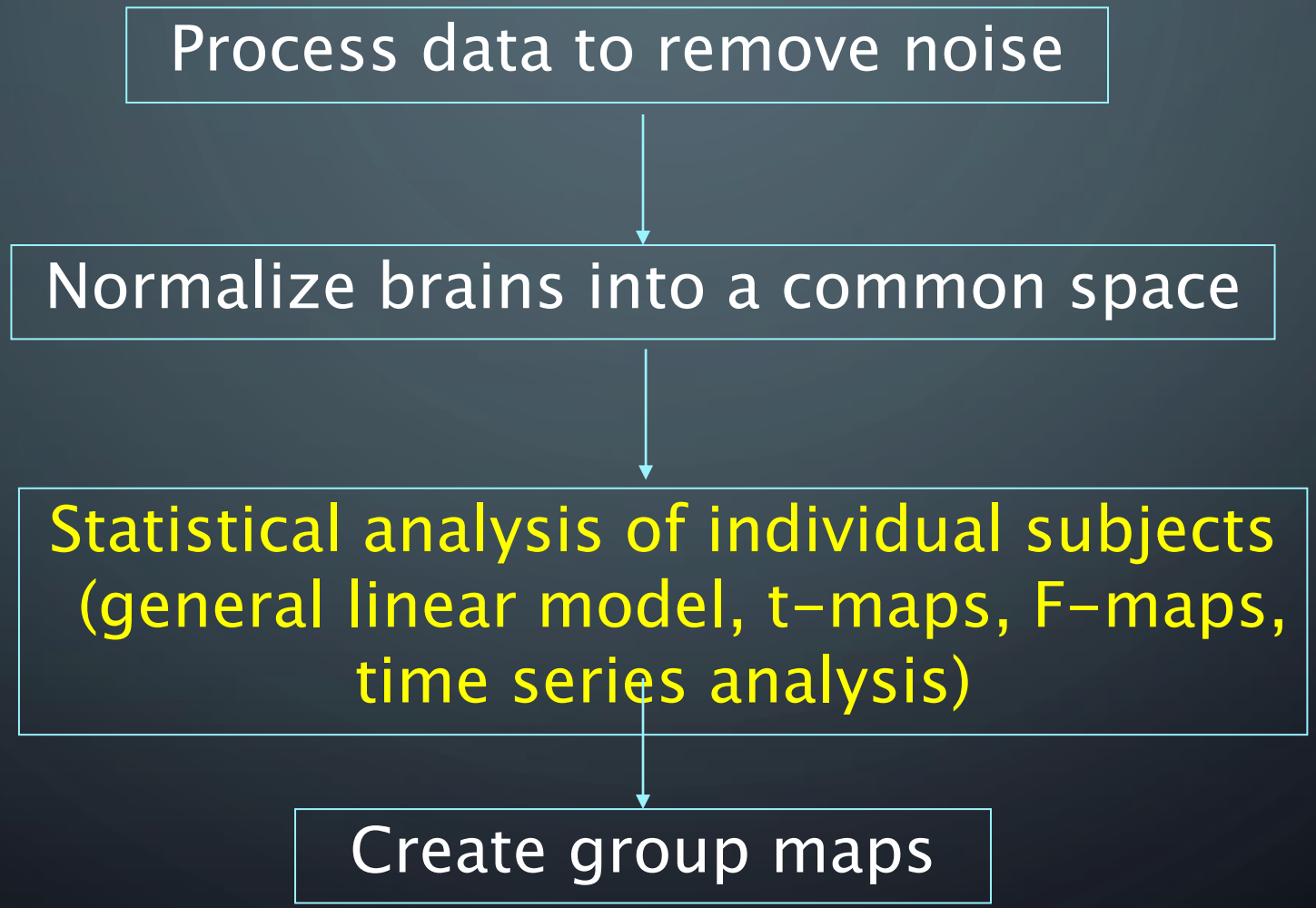
NOVEMBER 15, 2016

# OVERVIEW

1. Overview/History of fMRI
2. How it Works /Basic Principles
   - The Blood Oxygen-Level Dependent Signal (BOLD)
   - How the BOLD signal is measured

1. How to collect the data/ Design of experiments
2. How to analyze the data
3. Group analysis
4. Limitations and problems

# EXAMPLE OF FMRI DATA ANALYSIS STEPS

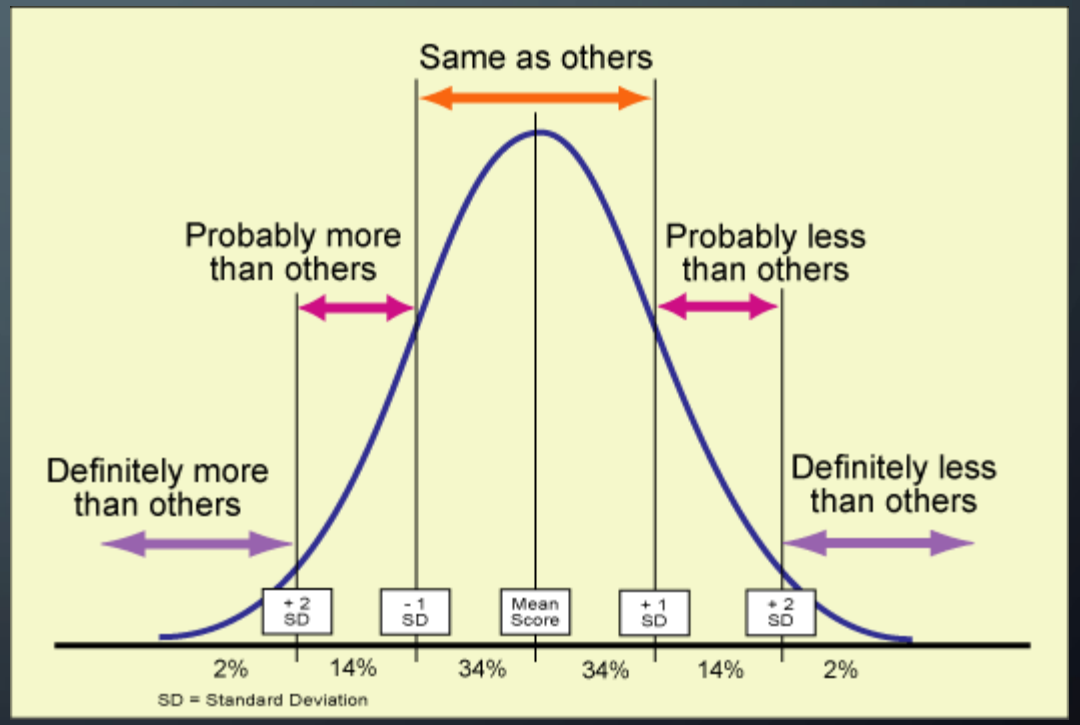


# WHAT CONSTITUTES ACTIVATION

- Statistics help us to answer the following:
  - How do we determine whether an area of the brain is activated by our task?
  - How confident are we that the areas we find are activated by our task?
  - Are the results in my group of subjects applicable to the wider population?
  - Are the differences between groups of subjects significant?

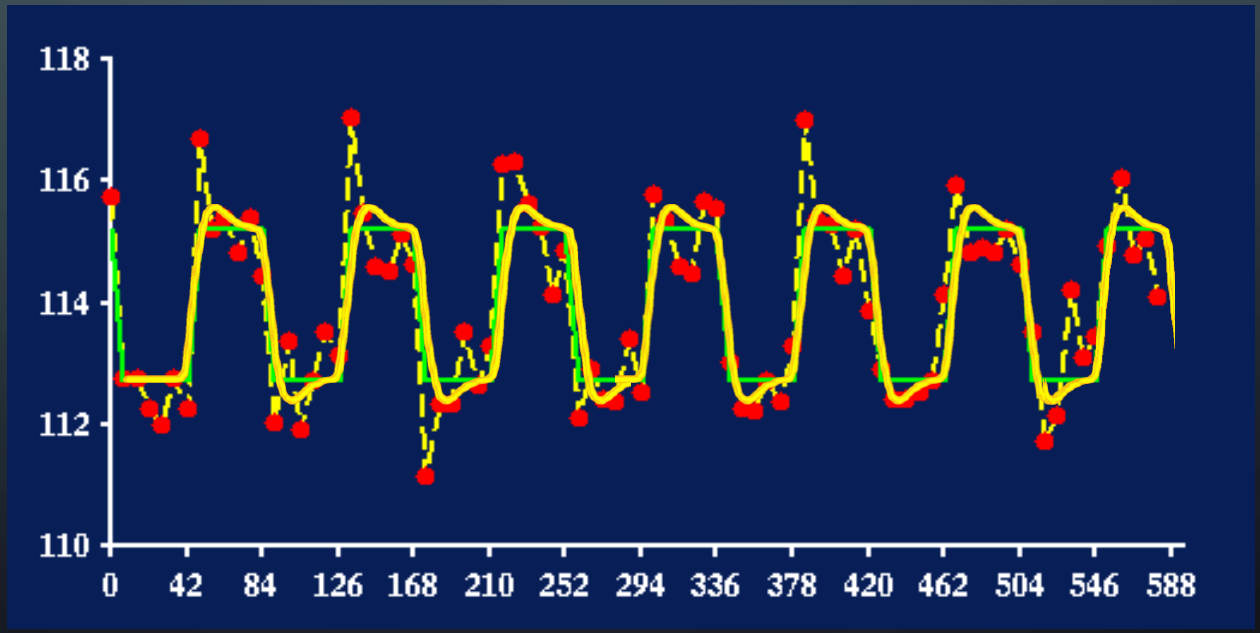
# “BRAIN ACTIVATION”

- We fit the general linear model (GLM) to each voxel in the brain
- Use the estimated model parameter to test for “activation”
- “Activation” means the voxel exceeded a certain threshold



# CORRELATION/REGRESSION

- Use a representative waveform representing the on-off periodicity of the design convolved with HRF and correlate that with MRI signal change across each of the scans



# GENERAL LINEAR MODEL & FMRI

How does GLM apply to fMRI experiments?

$$Y = X \cdot \beta + \epsilon$$

Observed = Predictors * Parameters + Error

BOLD = Design Matrix * Betas + Error

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# SIMPLE FMRI GLM

- x(t) is the block design convolved with a model of the HRF

$$y(t) = \beta x(t) + \varepsilon(t)$$

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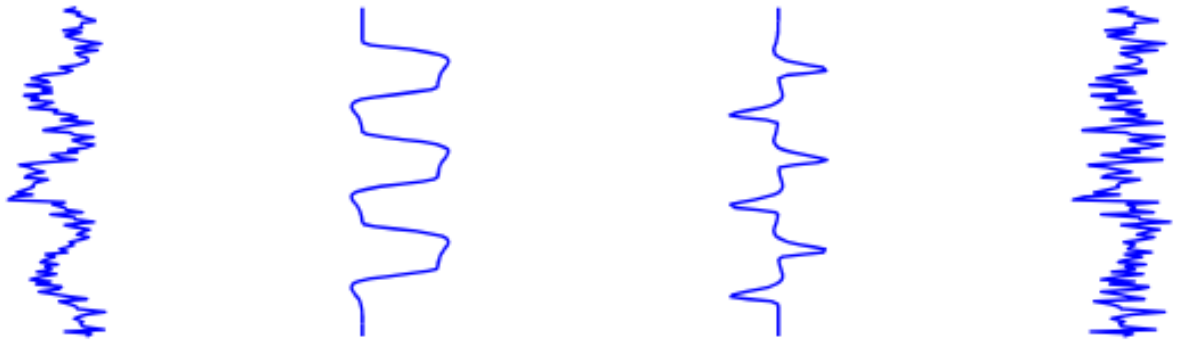
# GLM – ADDING REGRESSORS

- $x_2(t)$ adds Temporal Derivatives – allows for shifts in transition points of block design

$$y(t) = \beta_1 x_1(t) + \beta_2 x_2(t) + \varepsilon(t)$$



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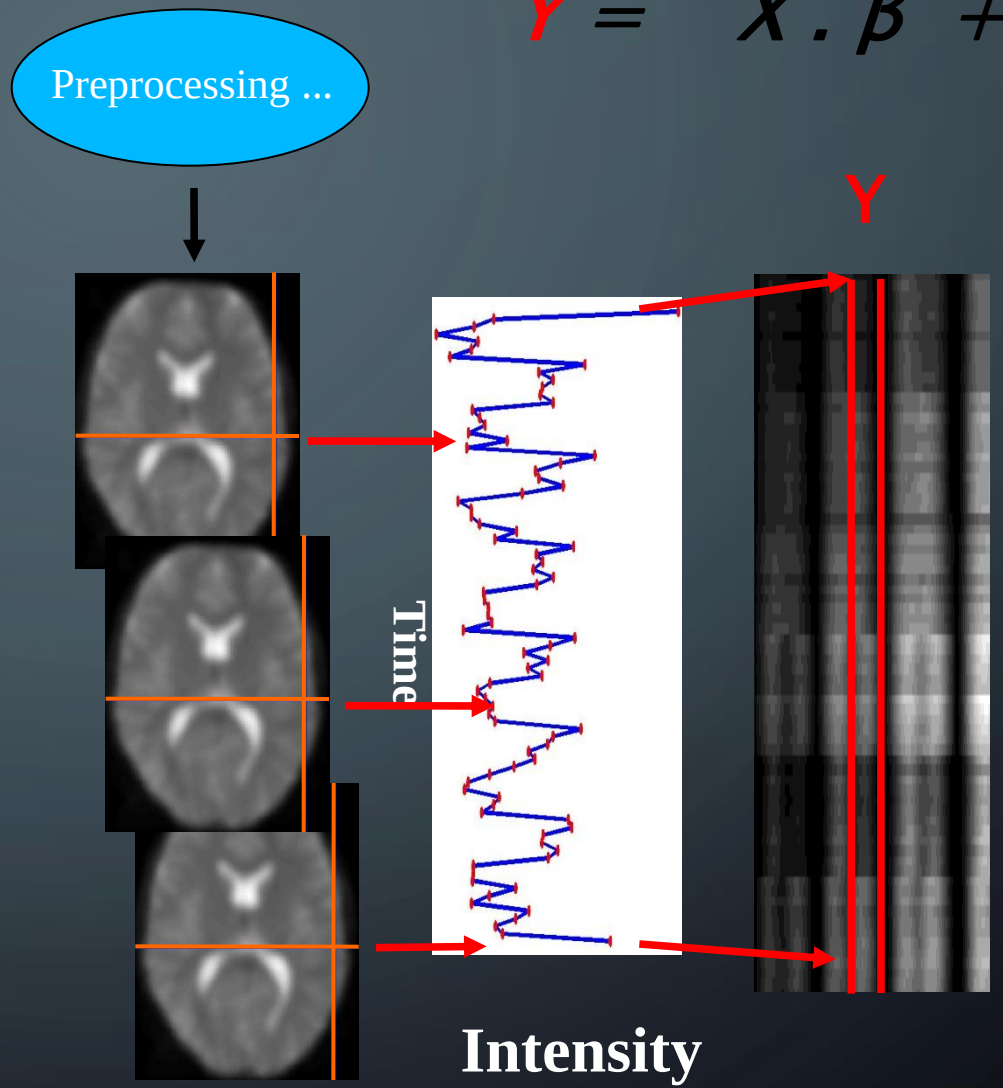
# Observed data

- Y is a matrix of BOLD signals:

- Each column represents a single voxel sampled at successive time points.

$$Y = X . \beta + \epsilon$$

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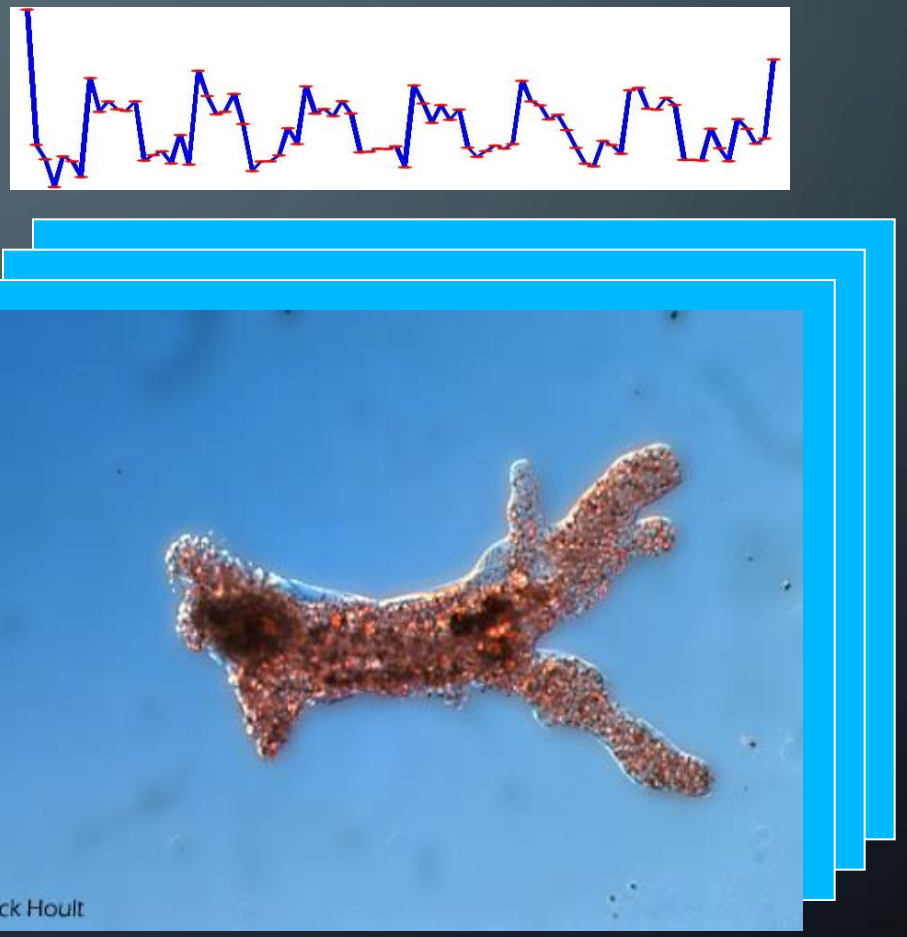
# UNIVARIATE ANALYSIS

$$Y = X . \beta + \epsilon$$

- Each voxel considered as independent observation
- Analysis of individual voxels over time, not groups over space
- SPM would still work on an Amoeba!

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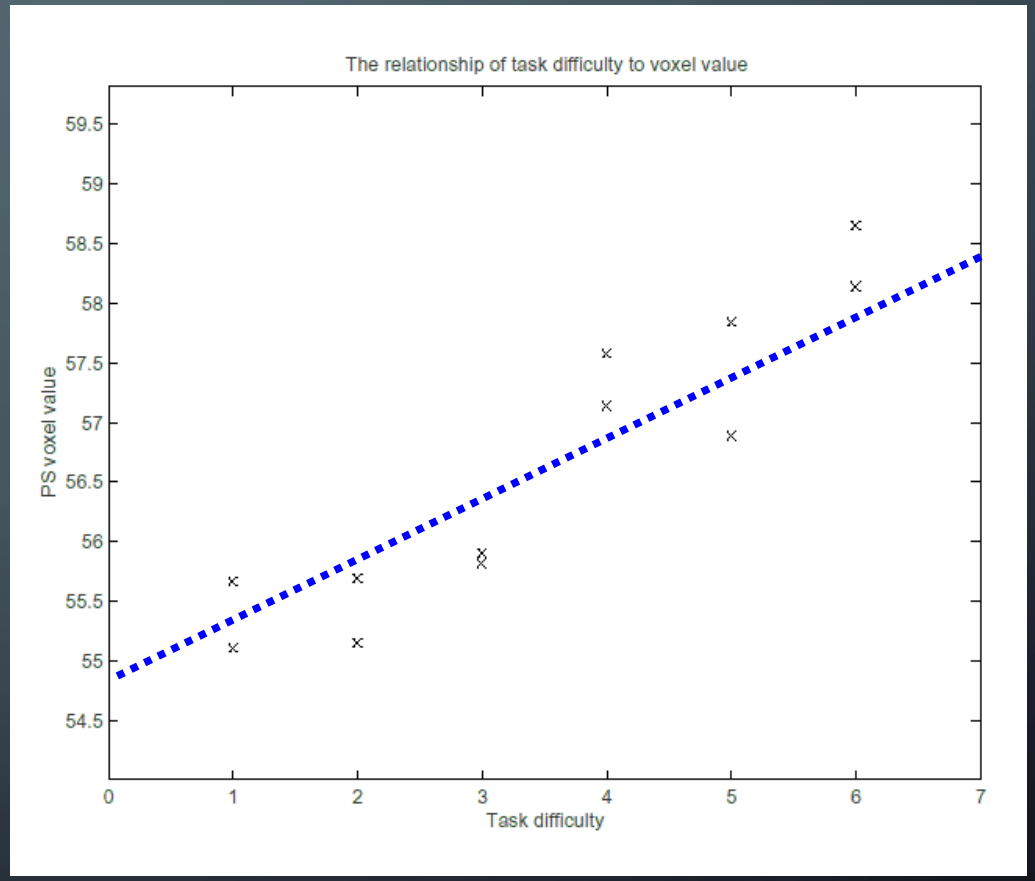
# CONTINUOUS PREDICTORS

$$Y = X . \beta + \epsilon$$

| | Y | X |
|---|---|---|
| **Scan no** | **Voxel 1** | **Task difficulty** |
| 1 | 57.84 | 5 |
| 2 | 57.58 | 4 |
| 3 | 57.14 | 4 |
| 4 | 55.15 | 2 |
| 5 | 55.90 | 3 |
| 6 | 55.67 | 1 |
| 7 | 58.14 | 6 |
| 8 | 55.82 | 3 |
| 9 | 55.10 | 1 |
| 10 | 58.65 | 6 |
| 11 | 56.89 | 5 |
| 12 | 55.69 | 2 |




X can contain values quantifying experimental variable

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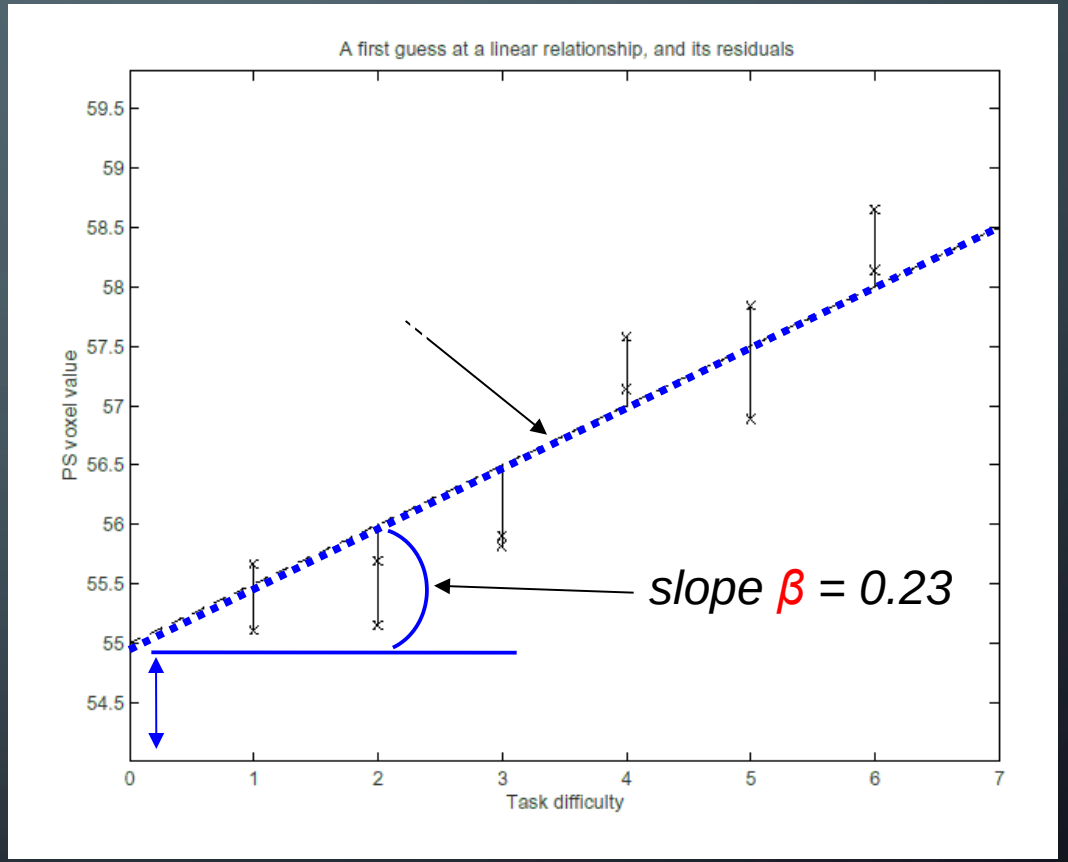
# Parameters & error

$$Y = X . \beta + \epsilon$$

- *β: slope of line relating X to Y*
  - *'how much of X is needed to approximate Y?'*
  - *the best estimate of β minimizes ϵ: deviations from line*

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# DESIGN MATRIX

$$Y = X . \beta + \epsilon$$

| | Y | $X^1$ | $X^2$ |
|---|---|---|---|
| Scan no | Voxel 1 | Task difficulty | Constant variable |
| 1 | 57.84 | 5 | 1 |
| 2 | 57.58 | 4 | 1 |
| 3 | 57.14 | 4 | 1 |
| 4 | 55.15 | 2 | 1 |
| 5 | 55.90 | 3 | 1 |
| 6 | 55.67 | 1 | 1 |
| 7 | 58.14 | 6 | 1 |
| 8 | 55.82 | 3 | 1 |
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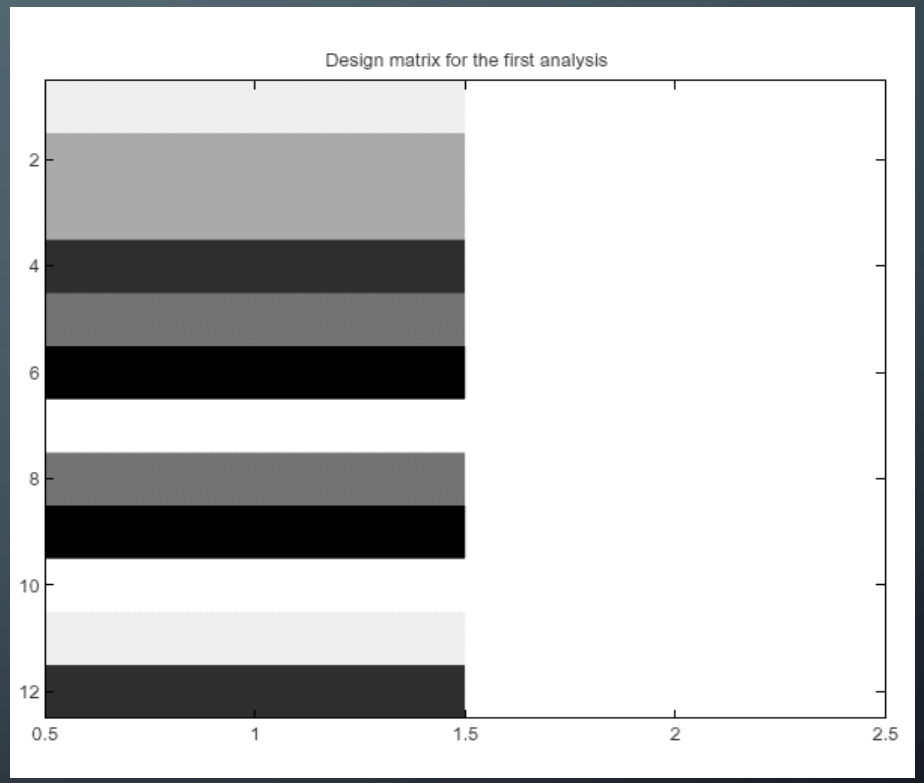
| 12 | 55.69 | 2 | 1 |

$X^1$ $X^2$




Matrix represents values of X

Different columns = different predictors

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# Matrix formulation

$$Y = X . \beta + \epsilon$$

$$\begin{pmatrix} Y_1 \\ Y_2 \\ Y_N \end{pmatrix} = \begin{pmatrix} X^1_{(t1)} & X^2_{(t1)} \dots & X^L_{(t1)} \\ X^1_{(t2)} & X^2_{(t2)} \dots & X^L_{(tS)} \\ X^1_{(tN)} & X^2_{(tN)} \dots & X^L_{(tN)} \end{pmatrix} \begin{pmatrix} \beta_1 \\ \beta_2 \\ \beta_L \end{pmatrix} + \begin{pmatrix} \varepsilon_{(t1)} \\ \varepsilon_{(t2)} \\ \varepsilon_{(tN)} \end{pmatrix}$$

$$\hat{Y}_1 = (5 * \beta_1) + (1 * \beta_2)$$

$$\hat{Y}_2 = (4 * \beta_1) + (1 * \beta_2)$$

…

$$\hat{Y}_N = (X^1_{(tN)} * \beta_1) + (X^2_{(tN)} * \beta_2)$$

| (t) | Y | $X^1$ | $X^2$ |
|---|---|---|---|
| time (t) | Voxel 1 | Task difficulty | Constant variable |
| 1 | 57.84 | 5 | 1 |
| 2 | 57.58 | 4 | 1 |
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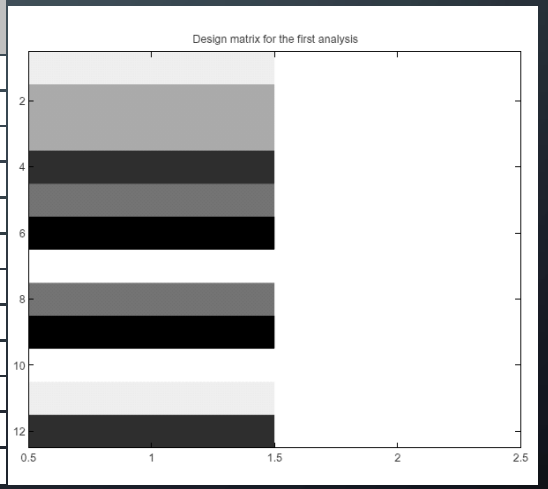
$X^1$ $X^2$

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## Parameter estimation and stats

- Find betas (by least squares estimation)
  - Y= βX -> "B = Y / X" (B= estimated *β)*
  - Matlab magic:

```
>> B = inv(X) * Y
```

- Now find error term:
  - *e = Y – (X * B )*
- ...and use these results for statistics:
  - *t = betas / standard error*

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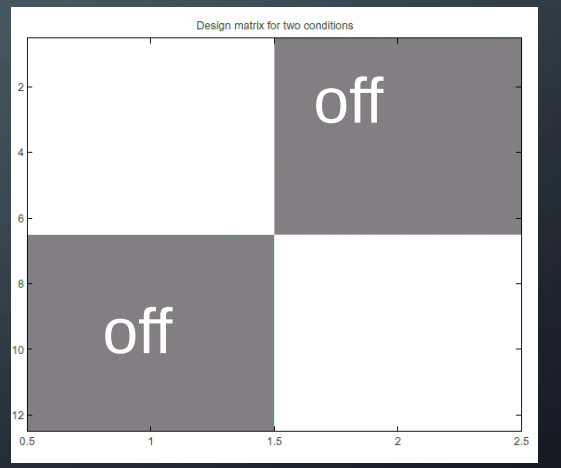
# Covariates vs. conditions

- **Covariates:**
  - parametric modulation of independent variable
  - e.g. task-difficulty 1 to 6 -regression: beta = slope

- **Conditions:**
  - specify time of onset and duration
  - e.g. integers 0 or 1: 'off' or 'on' -> ANOVA: beta = effect mean

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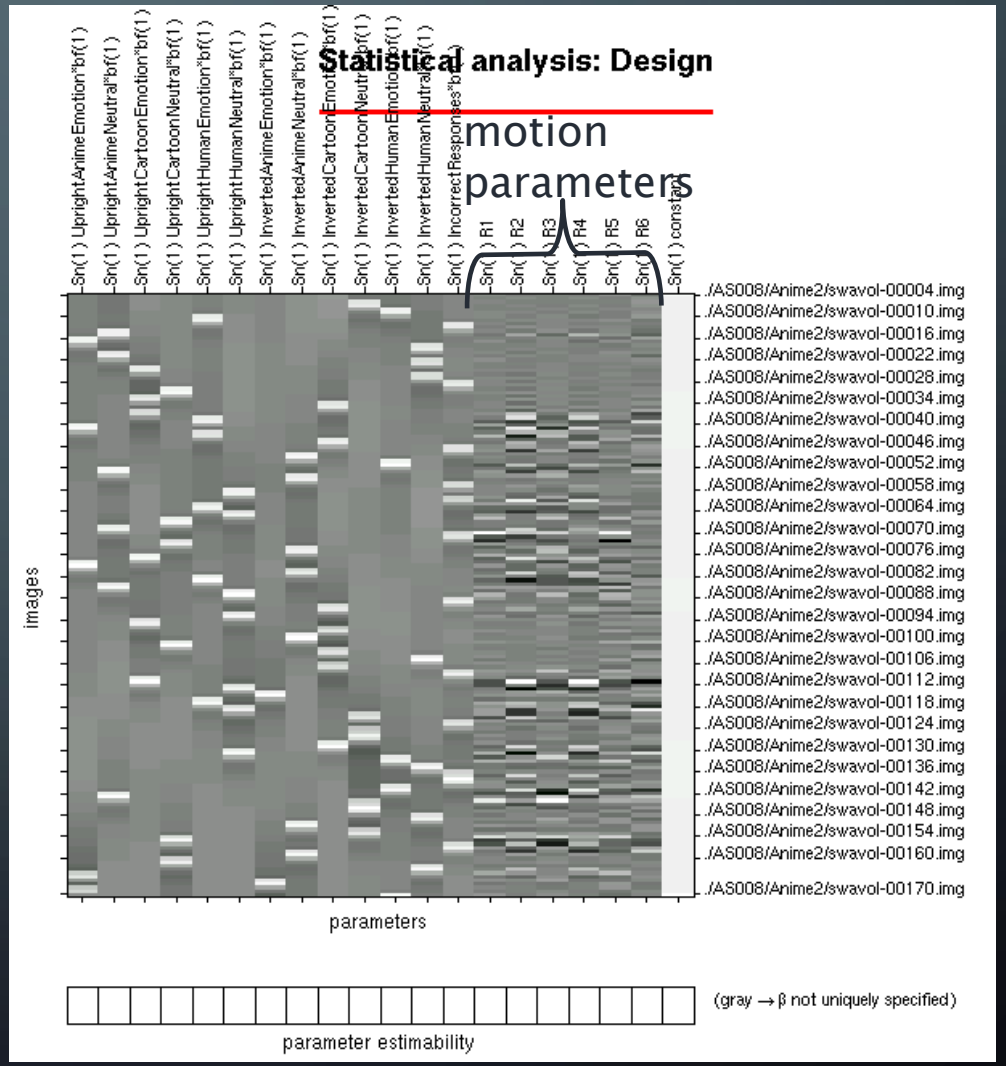
# DESIGN MATRIX WITH MOTION AS REGRESSORS

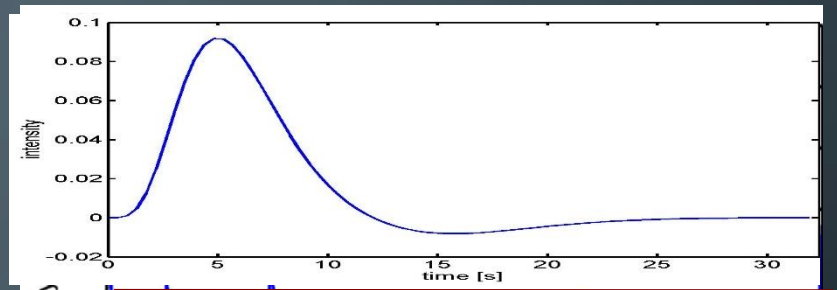
- Example includes transformation parameters from motion correction as nuisance regressors
  - Useful for removing noise due to head motion
  - However, if motion is correlated with task then this will reduce statistical significance

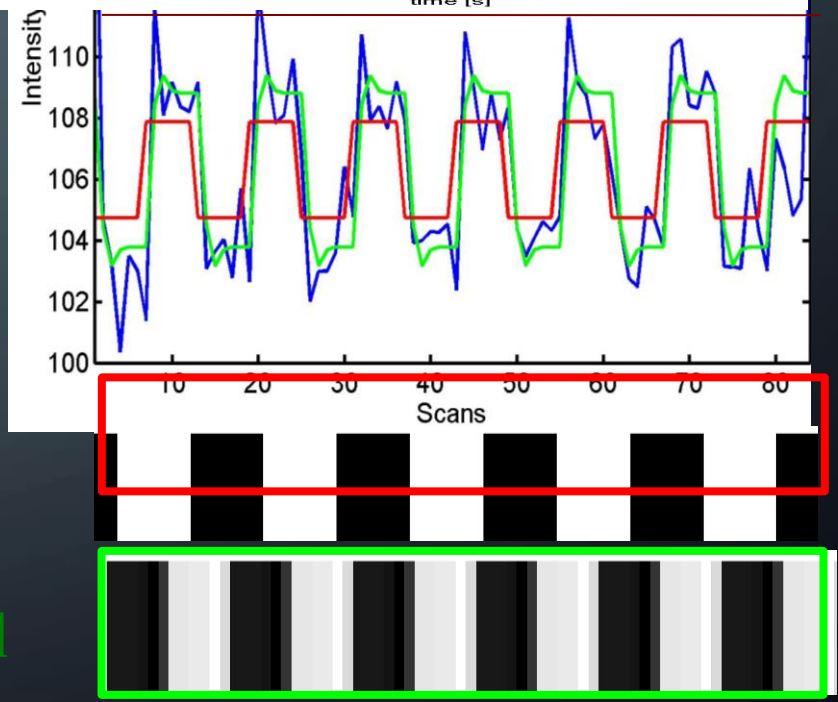


# MODELLING HEMODYNAMICS

- Brain does not just switch on and off!
- Reshape (convolve) regressors to resemble HRF

HRF basic function

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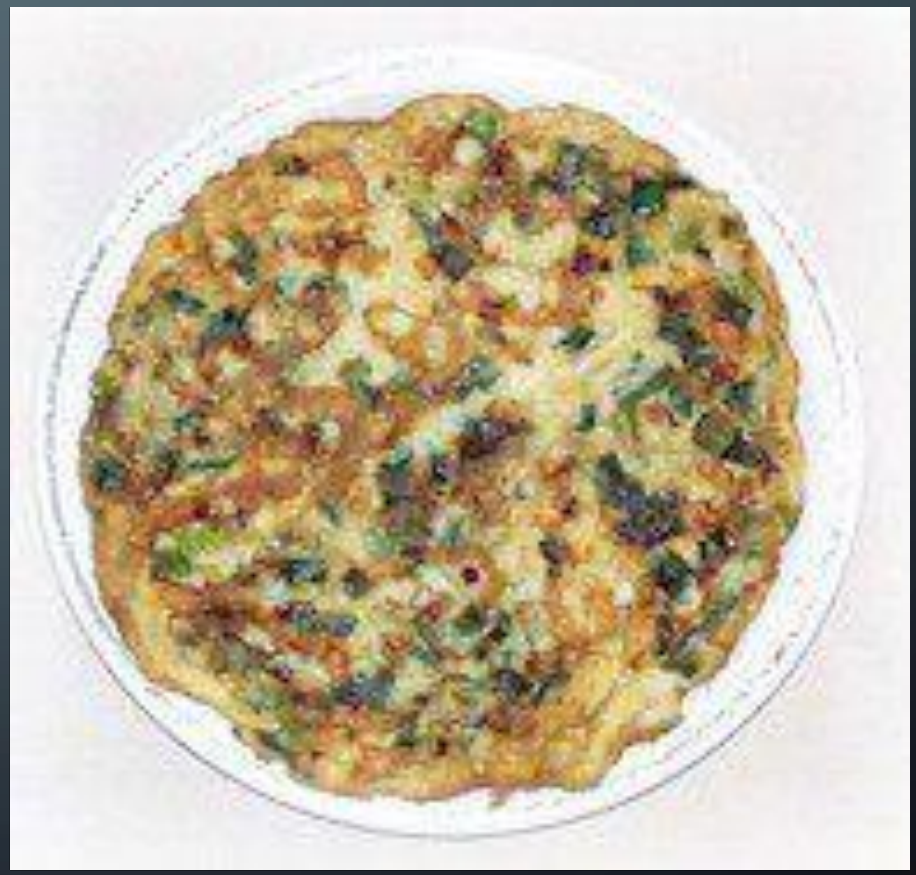
# SUMMARY: REVERSE COOKERY

- You start with the finished product and want to know how it was made
  - You specify which *ingredients* to add (*design matrix variables*)
  - For each ingredient, GLM finds the *quantities* (*betas*) *that produce the best reproduction* (*model*)
  - Now you can compare your recipe with others (*null hypothesis*) to see if they differ! (*statistical tests*)



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# FORMAL STATEMENT OF A HYPOTHESIS

- Research question is framed as a hypothesis
- Null hypothesis assumes that the hypothesis is not true
- Statistics aim to disprove the null hypothesis and thus accept the research hypothesis
- In fMRI we are testing difference in BOLD signal between two conditions

$H_1$: $Condition_1 \neq Condition_2$

$H_0$: $Condition_1 = Condition_2$

# FMRI EXAMPLE

- Hypothesis: “Moving the thumb will cause an increase in neuronal activity which we detect with BOLD signal changes”
- Null Hypothesis: “Moving the thumb will ***NOT*** cause an increase in neuronal activity which we detect with BOLD signal changes”
  - Experimental condition – moving thumb
  - Control condition – thumb not moving
  - Outcome measure – MRI signal changes

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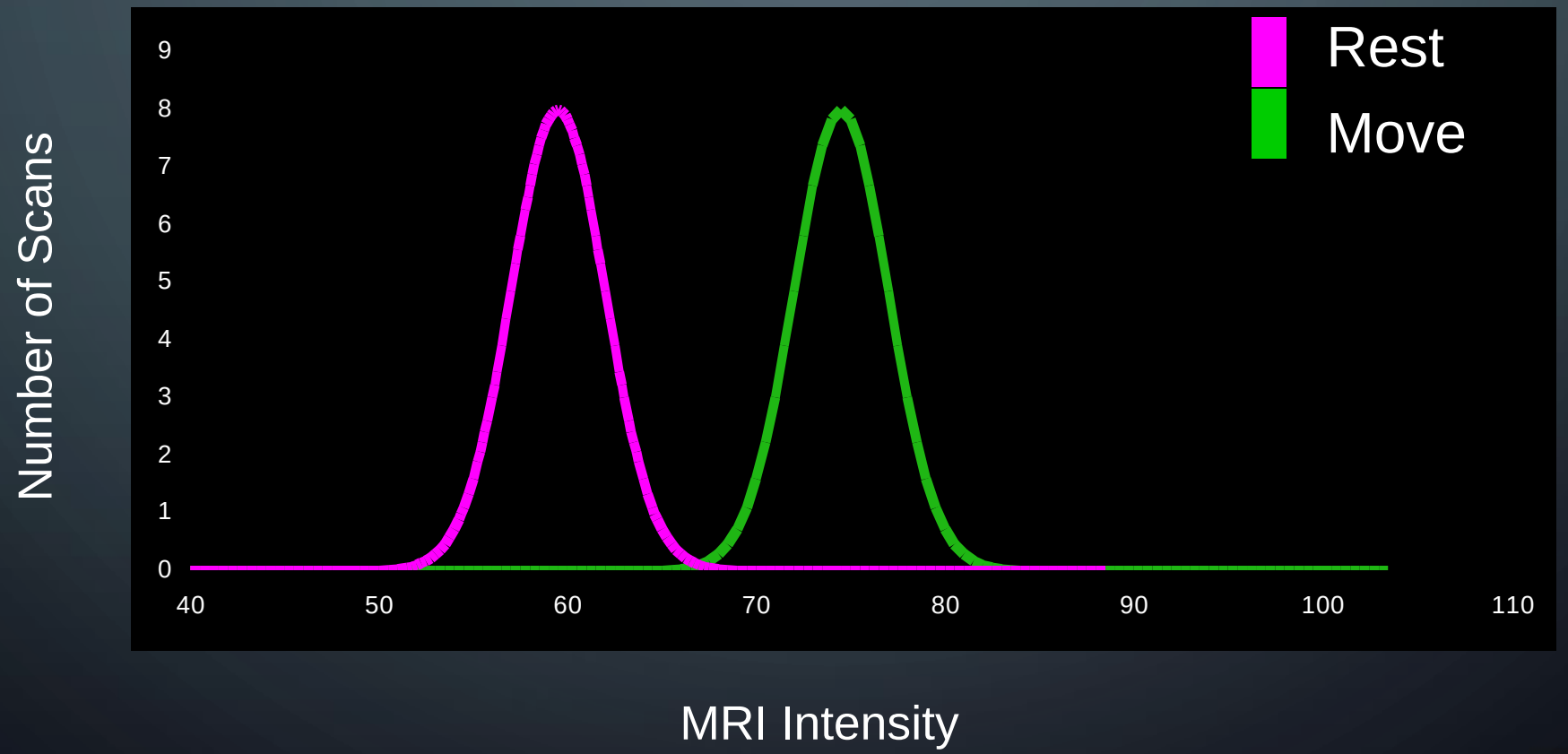
# HYPOTHESIS TESTING

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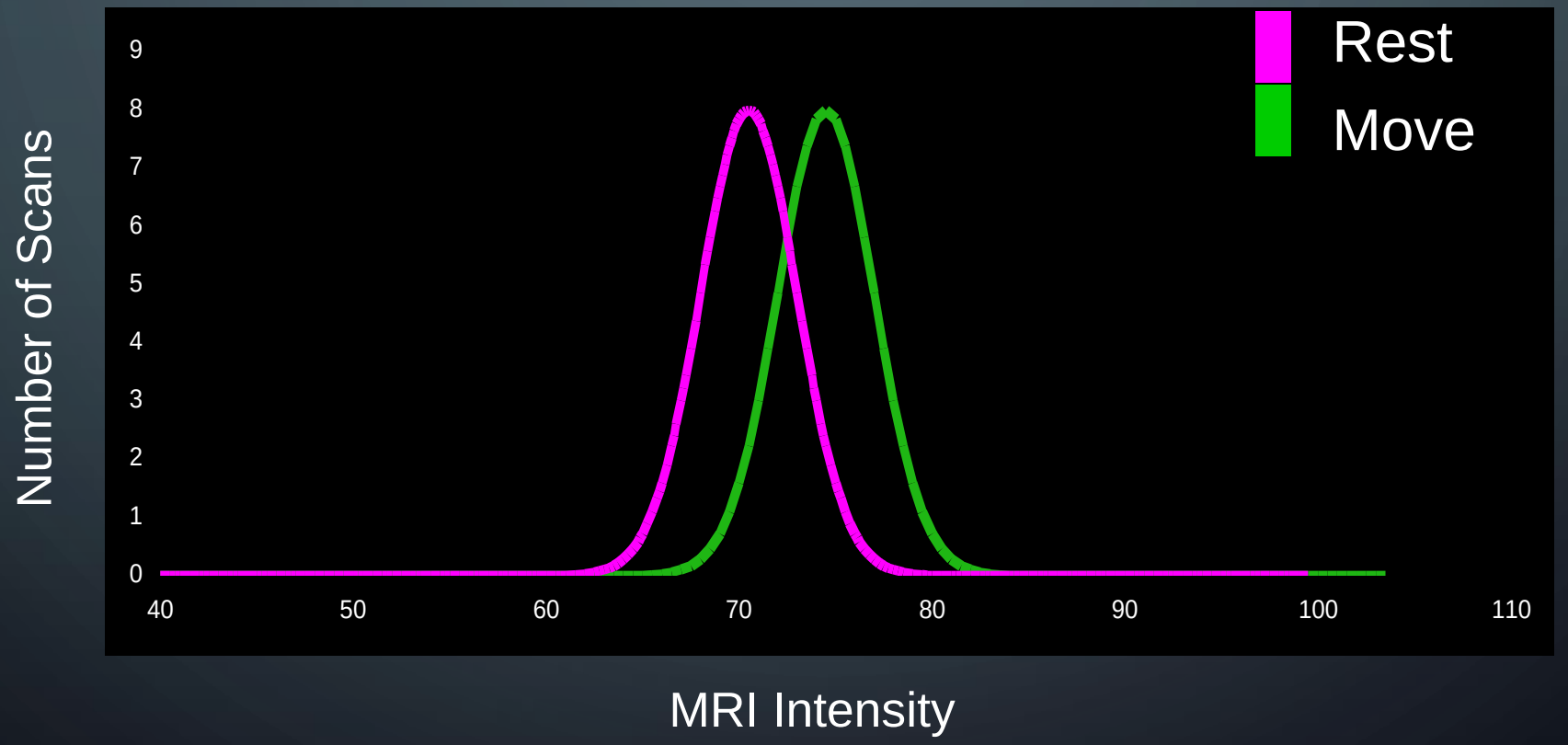


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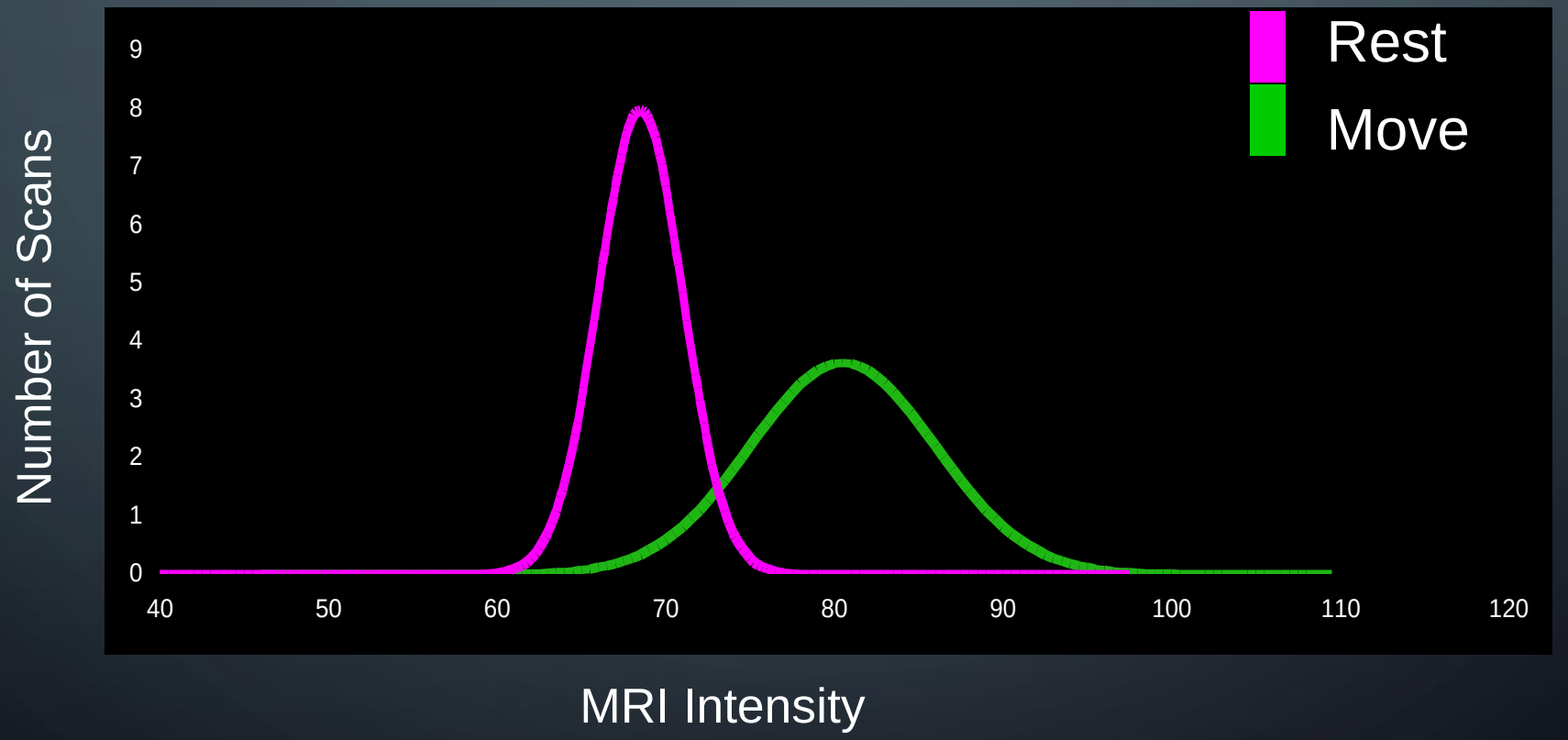


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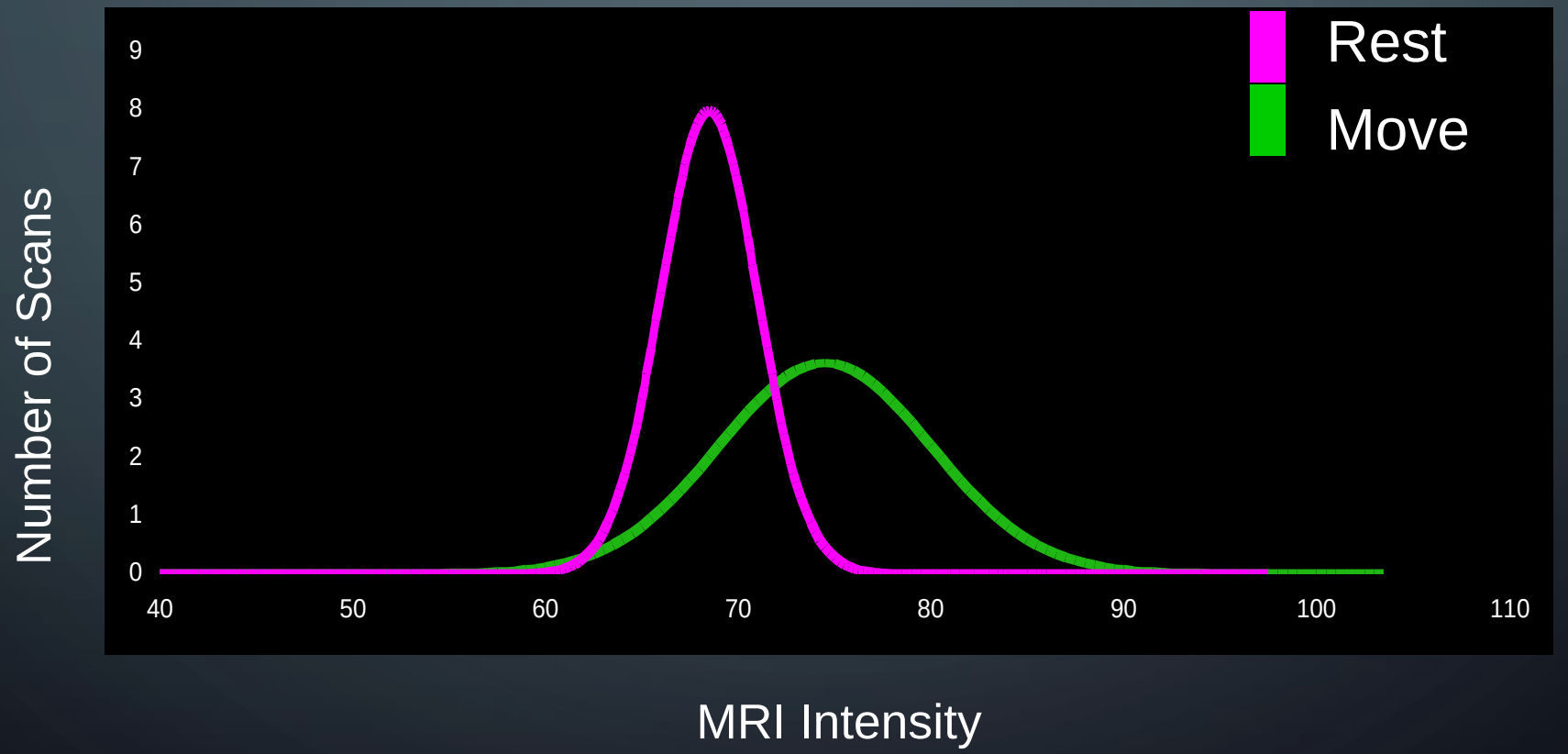
# HYPOTHESIS TESTING

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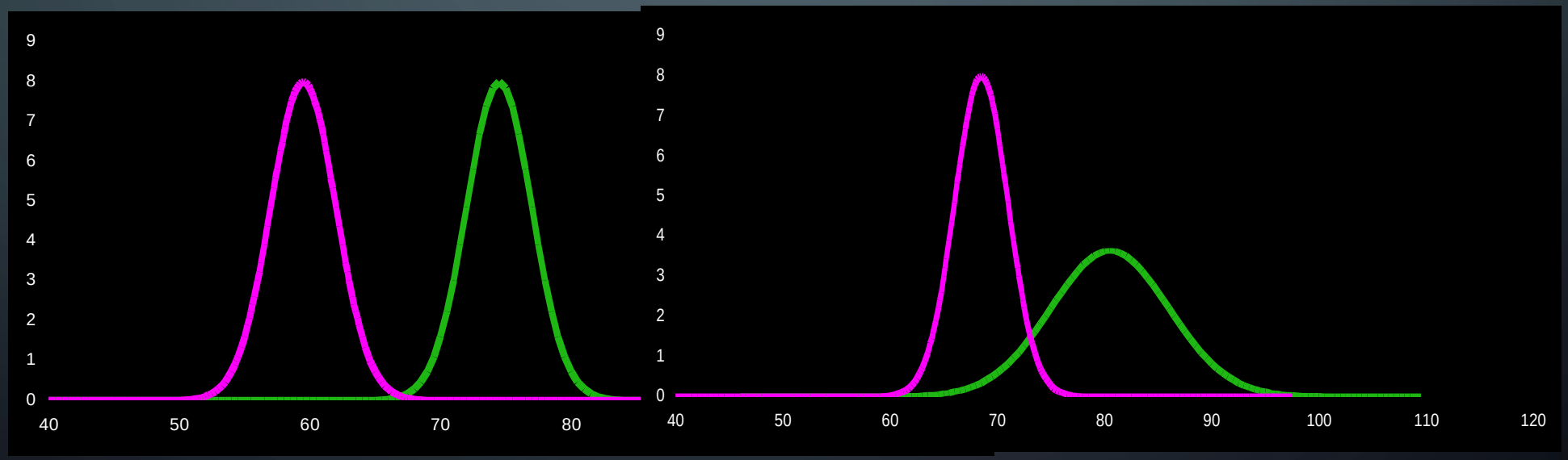
# HYPOTHESIS TESTING

- Two factors describe how much effect the experimental condition had:
  - Difference between the mean intensities of each condition
  - Degree of overlap in intensities

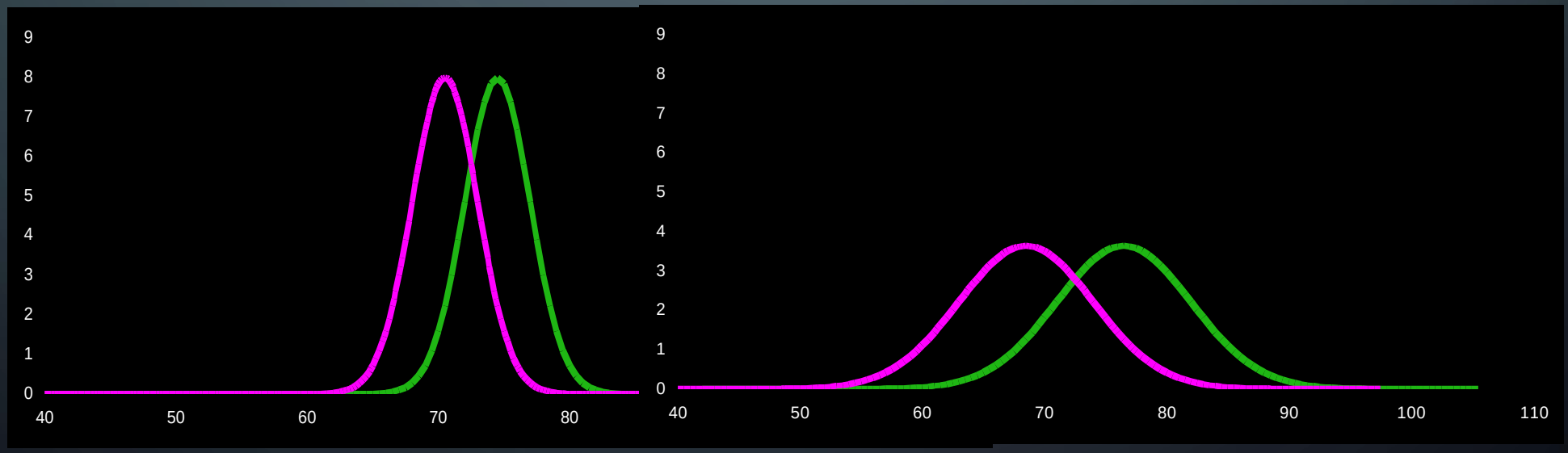
# HYPOTHESIS TESTING

- Experimental condition has an effect



# HYPOTHESIS TESTING

- Experimental condition has *no* effect

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# THE T-TEST

- Formally incorporates our intuitive sense of when there is an effect
- Based on a measure of the distance between the two means and the spread of each condition

$$t = \frac{(m_1 - m_2)}{\sqrt{(\sigma_1^2 + \sigma_2^2)}}$$

- We use our Beta values in these statistical measures!

# T-STATISTICS AND P-VALUES

- The p-value for a t-statistic gives the probability that the difference between the experimental and control conditions arose by chance
- Typically $p < 0.05$ is considered minimum cut-off for significance (i.e. alpha is set at $p < 0.05$)
- Statistics tables list the p-values for each t-statistic based on the df, degrees of freedom, (single subject analysis df=total number of scans minus 1)

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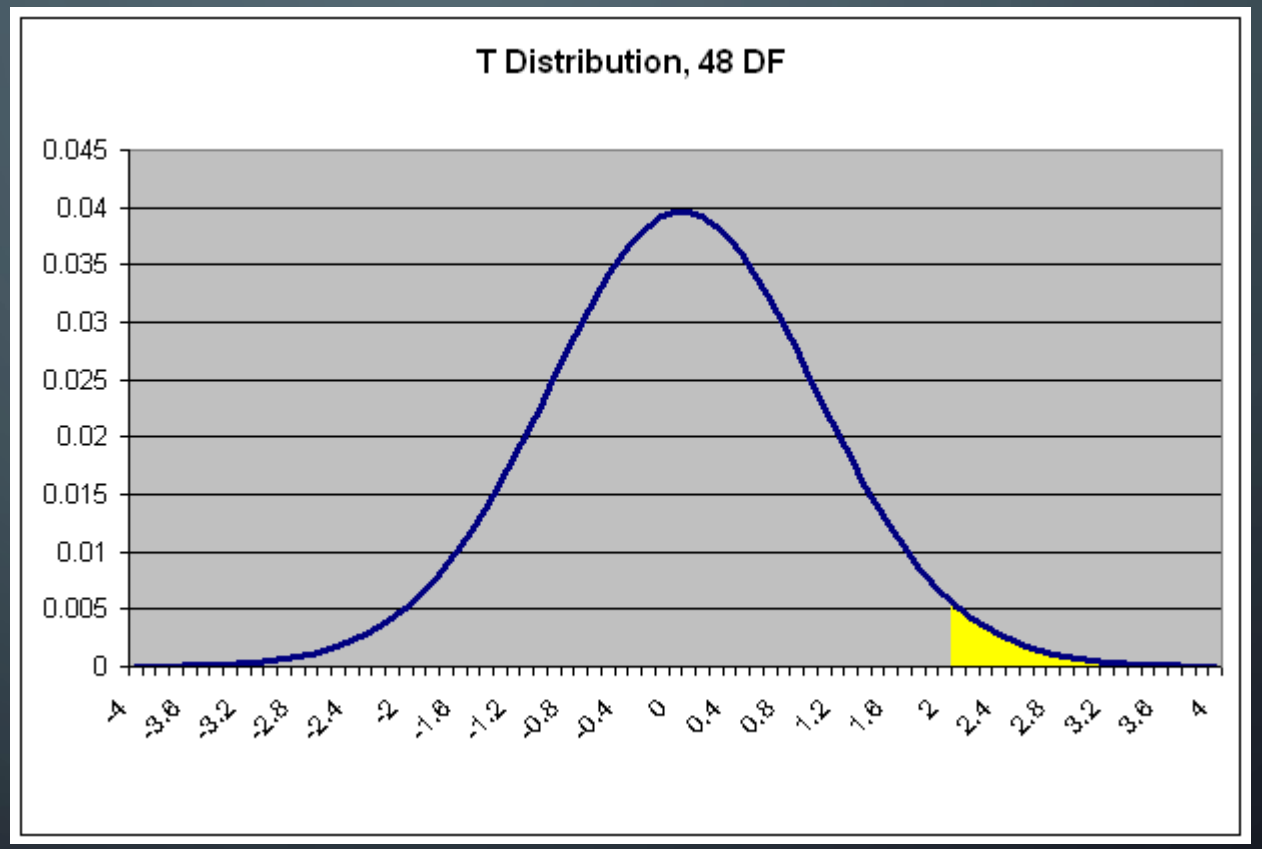
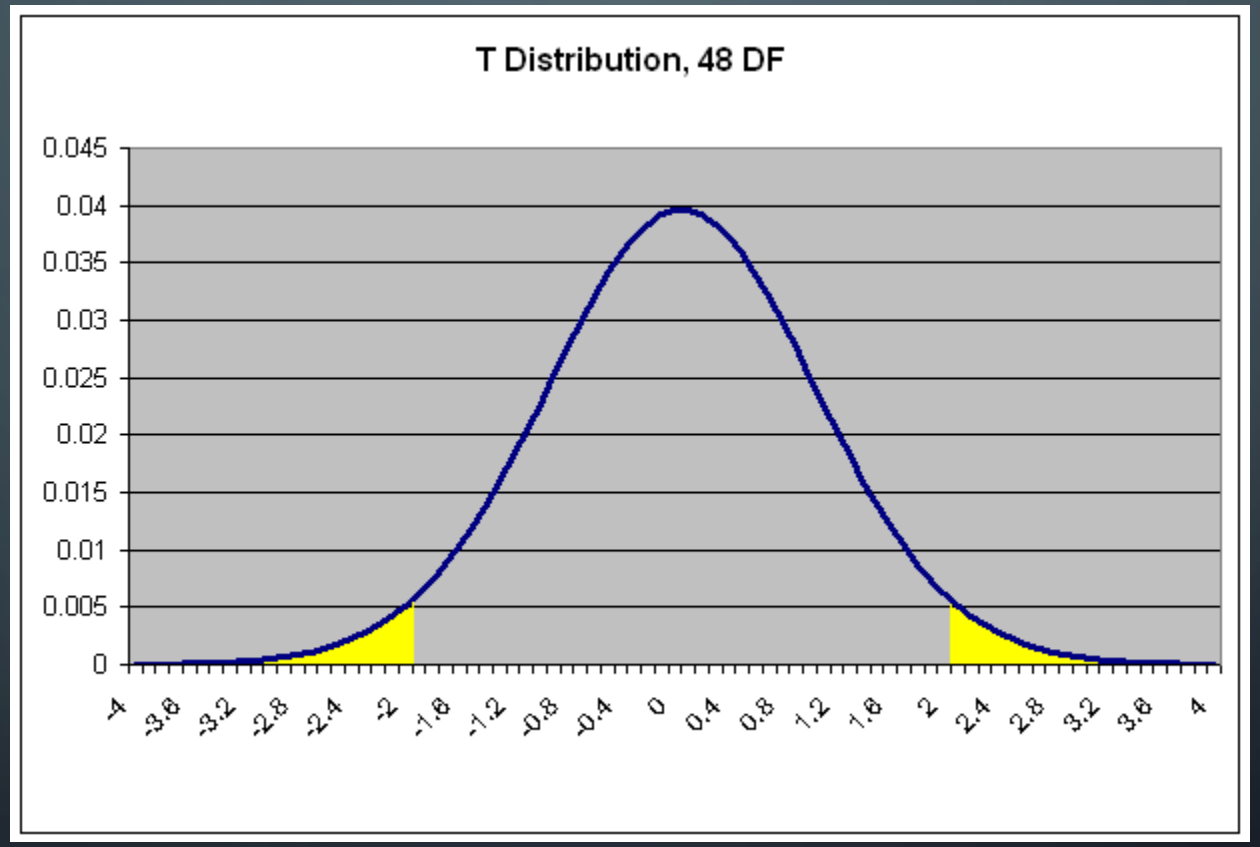
# ONE-TAILED TEST




Yellow area under the curve is about 0.025 (for t=2).

# TWO-TAILED TEST




Yellow area under the curve is about 0.05 (for t=2).

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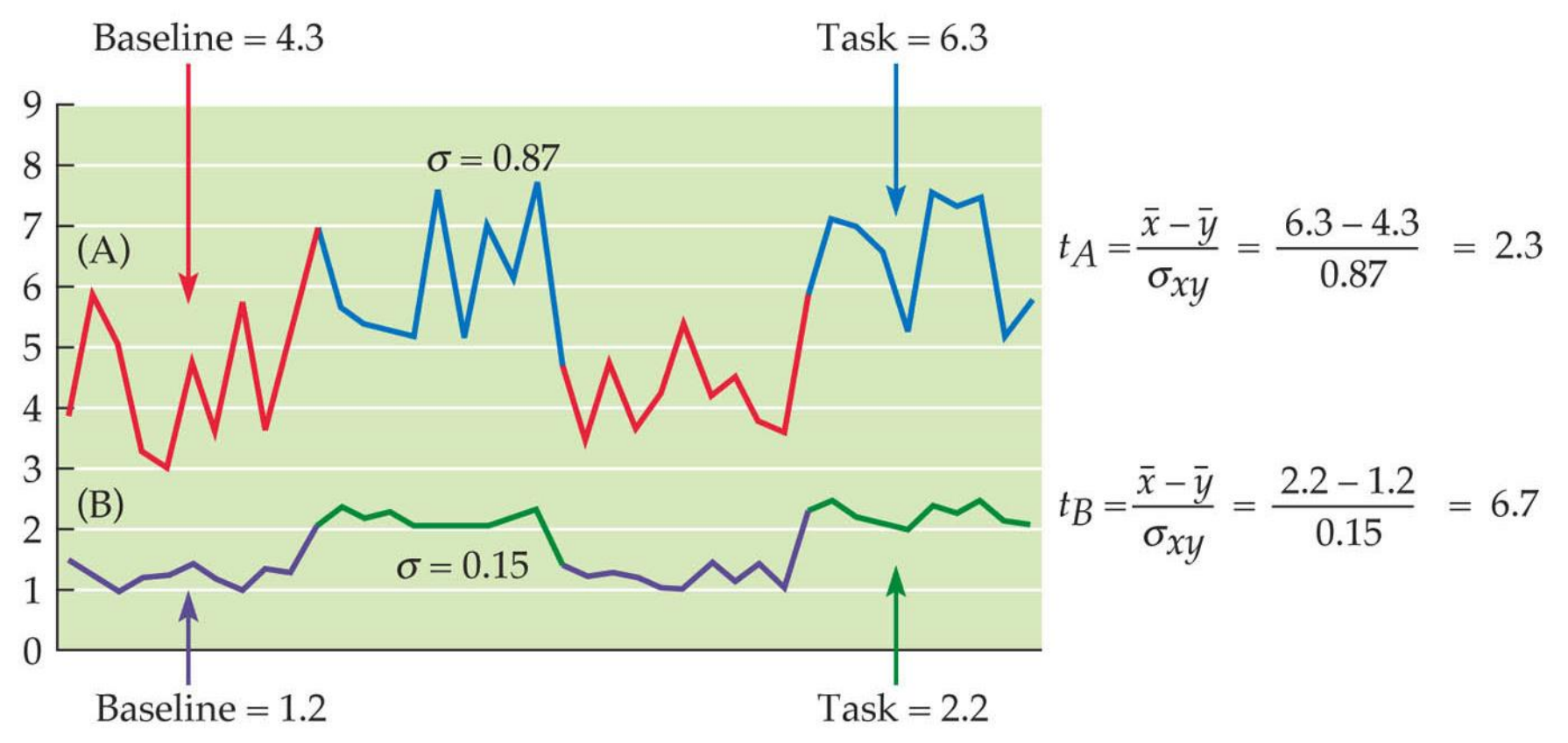
# T-STATISTICS AND P-VALUES

Ex.

Suppose we find a voxel in which the t-statistic is 3.3 and there were 20 scans at rest and 20 scans while moving thumb.

The probability that the difference in the MRI signal in this voxel *is not due* to the movement of the thumb is 0.002 two-tail or 0.001 one-tail.

# EXAMPLES OF THE AFFECT OF VARIANCE



# T-STATISTICS, P-VALUES, & Z-SCORES

- Unlike t-statistics, the p-value for Z-scores, which are based on the normal distribution, does not change depending on the number of scans
- In functional imaging it is common to convert the t-statistic to a Z-score since it is easier to compare across studies (not dependent on degrees of freedom)

# PROBLEMS WITH THE T-TEST

- Systematic differences such as artifacts can create apparent significant differences where none exists
- Disregards any temporal characteristics of the data since only means are compared
- Assumption of t-test is that the data for both conditions is normally distributed – usually though not always true
  - Smoothing helps make data normally distributed

# MAKING ERRORS

- Two types of errors:
  - Type 1:  Activation is true, but we mistakenly reject it (False positive)
  - Type II:  Activation is false, but we fail to reject it (False negative)

| | Disease or Condition | No Disease or Condition |
|---|---|---|
| Test Positive | A<br>True Positive | B<br>False Positive |
| Test Negative | C<br>False Negative | D<br>True Negative |

# MULTIPLE COMPARISON PROBLEM

- If more than one hypothesis test is performed, chance of making errors is even greater
- The more tests performed, the greater the likelihood of errors
- Say we have 32 slices, 64x64 voxels in xy plane
- If we test 64x64x32= 131,072 comparison tests!!!
- Which voxels are actually significant?
- Want to balance sensitivity (true positive rate) and specificity (true negative rate)

# MEASURE OF FALSE POSITIVES

- There are ways to quantify the amount of false positives
  - Family Wise Error Rate (FWER) – control the probability of false positives
  - False Discovery Rate (FDR) – control the proportion of false positives among rejected tests

# FAMILY-WISE ERROR RATE

- Control the probably of making one or more Type I errors in a family of tests
- Basically adjusting p-values for the number of hypothesis tests performed
- FWER controlling methods include:
  - Bonferroni correction
  - Random Field Theory
  - Permutation tests

# How to avoid false associations?

Applying ***m*** independent statistical tests with significance level a, a probability of at least one false association should be

$1-(1-a)^m < 0.05$

$$a = 1-(1-0.05)^{1/m} \approx \frac{0.05}{m}$$

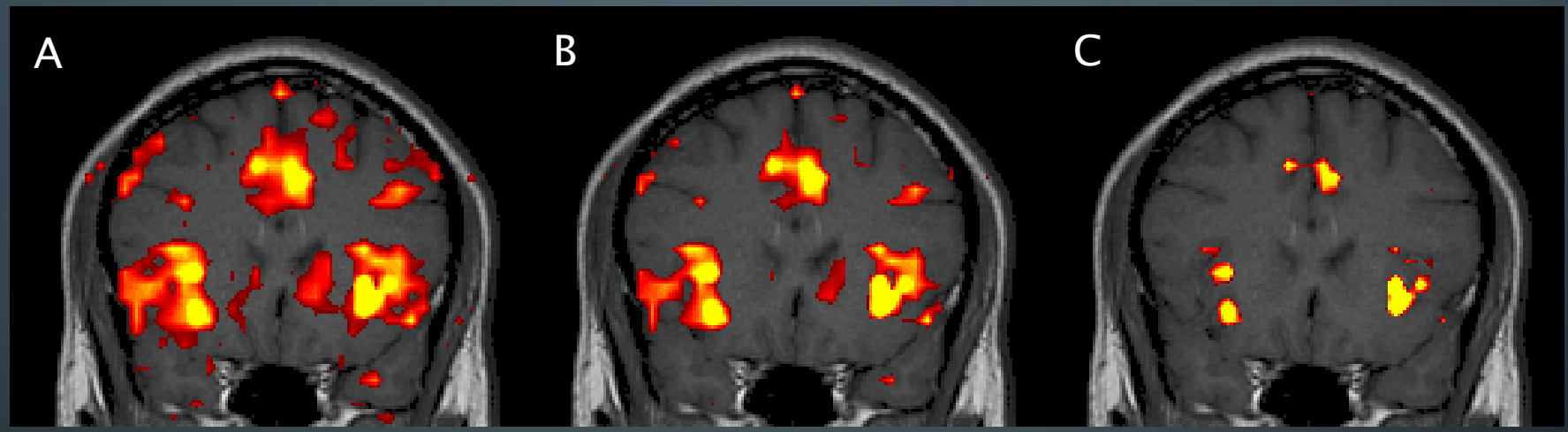
## Carlo Bonferroni (1935):

When applying ***m*** independent statistical test, only significant results are results with

$$p < \frac{0.05}{m}$$

# BONFERRONI CORRECTION

- Very simple method for ensuring that the overall Type I error rate of $\alpha$ is maintained when performing m independent hypothesis tests
- Rejects any hypothesis with p-value $\leq \alpha/m$:
- For example, if we want to have an experiment wide Type I error rate of 0.05 when we perform 10,000 hypothesis tests, we'd need a p-value of $0.05/10000 = 5 \times 10^{-6}$ to declare significance
- Problem: Extremely conservative – often fail to find results




*t = 2.10, p < 0.05 (uncorrected)*

*t = 3.60, p < 0.001 (uncorrected)*

*t = 7.15, p < 0.05, Bonferroni Corrected*

# FALSE DISCOVERY RATE (BENJAMINI, HOCHBERG, 1995)

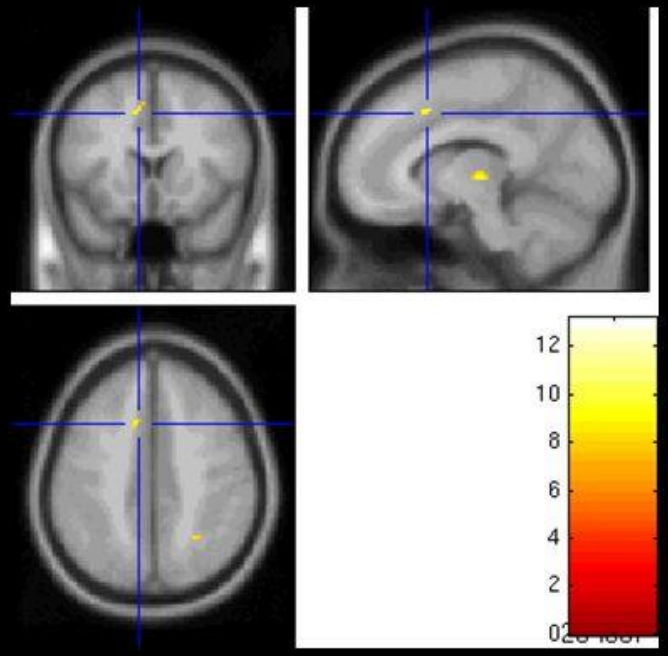
- Order tests according to p-value :
- $p_1 < p_2 < \ldots < p_m$.

- For FDR control on α level (e.g. 0.05),

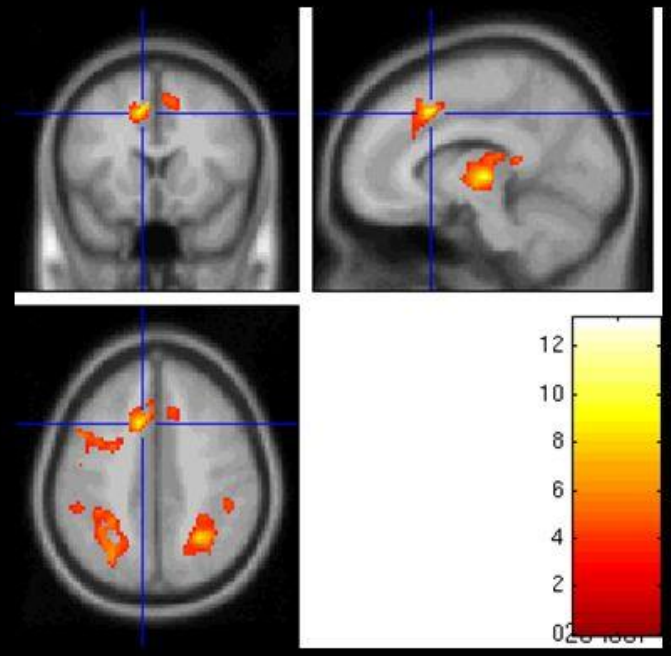
  we find $$j^* = \max\left\{ j : p_j \le \frac{j}{m}\alpha \right\}$$

- Differences are assumed to be significant for j = 1, …, j*.
- For $j > j^*$ differences are assumed not to be significant

# FWE vs FDR Working Memory Example




FWE Perm. Thresh. = 7.67
58 voxels




FDR Threshold = 3.83
3,073 voxels

# ANALYSIS OUTPUTS

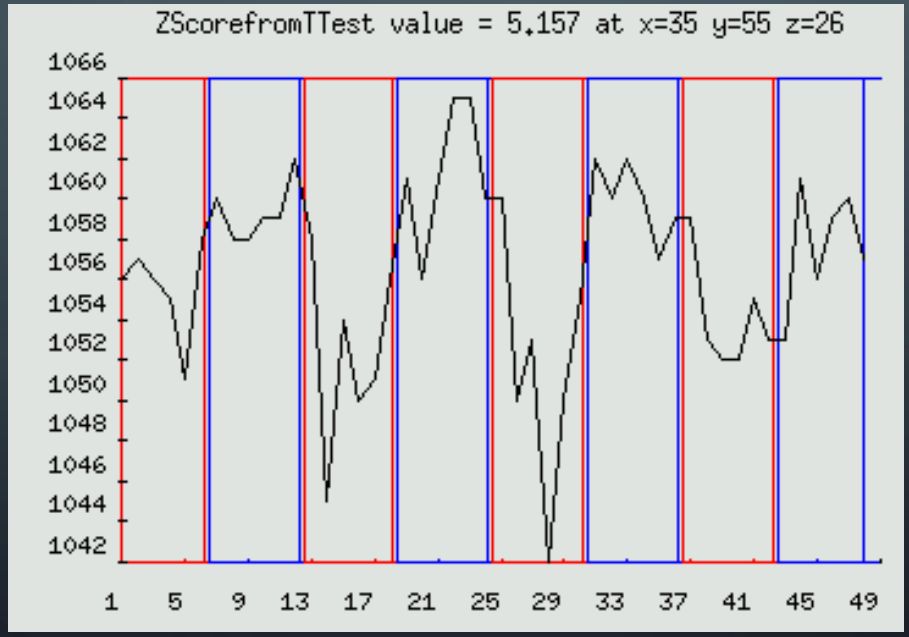
- Output from analysis software will typically include some visual representation of the results and tables of areas of activation
- Variety of tools available to interrogate and visualize results

# LOCAL MAXIMA REPORTING

- Utility that generates a list of coordinates that correspond to the highest values in the statistical map grouped by ‘cluster’
- Clusters are defined by spatially contiguous set of voxels above a statistical threshold (p-value)
- SPM reports the maxima within each cluster and up to 2 sub-maxima at least 8 mm from the other maxima

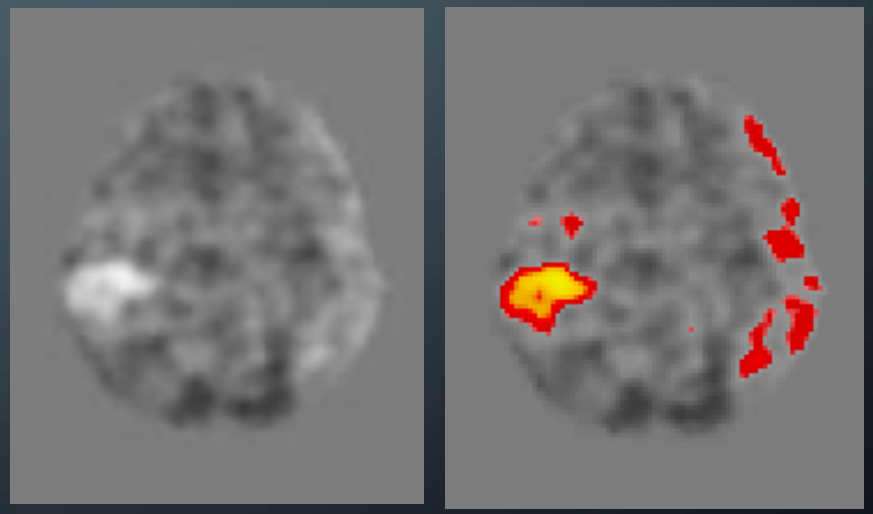
# VOXEL SURFING/PLOTTING

- Used to examine how well the changes in the MRI signal follow the on-off characteristics of the task



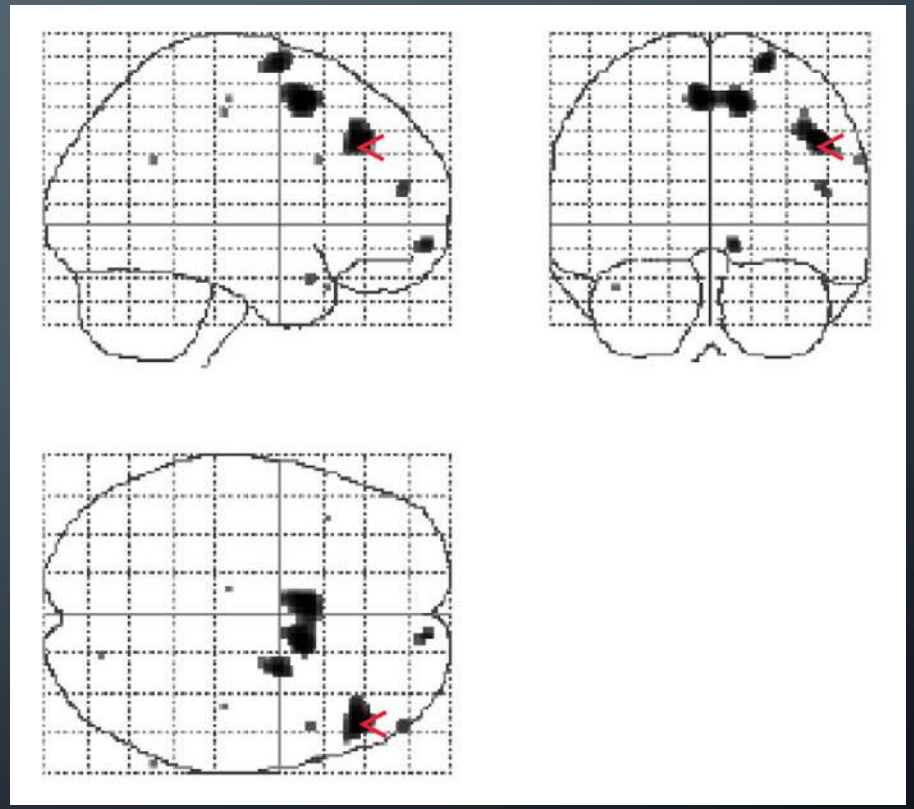
# BASIC DISPLAY OF RESULTS

- Simply display all of the t-statistics or other statistic in gray scale or with color coding
- Useful for getting an overall sense of the results
- Can see the data in its most basic form
- Use threshold of 0.1 or higher in SPM to get similar type of display



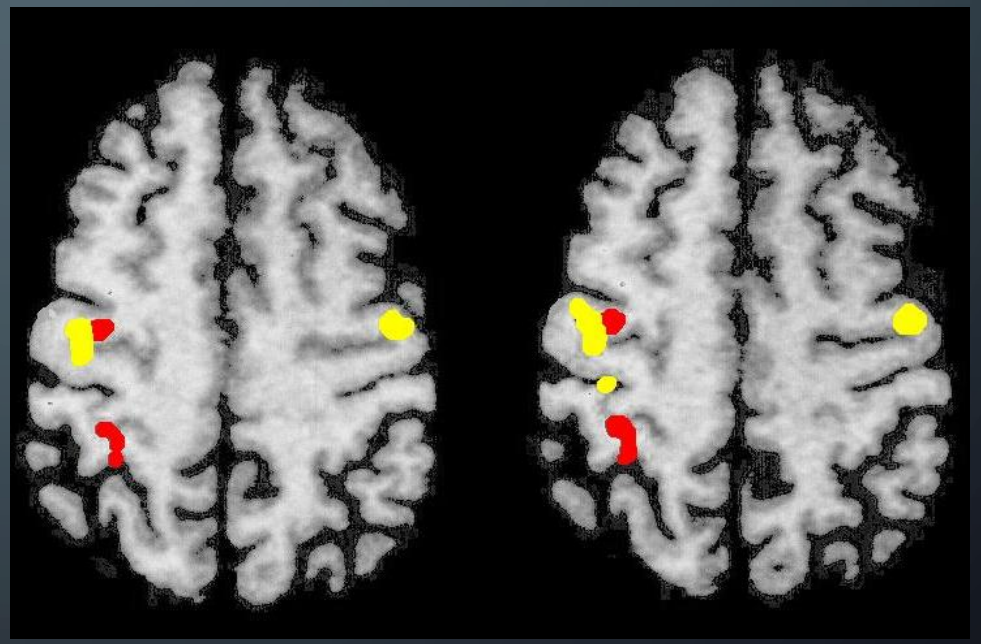
# GLASS BRAIN (SPM)

- Glass brain is a maximum intensity projection (MIP) generated for all three orthogonal planes
- Quick way to see what is activated when there are only a few areas



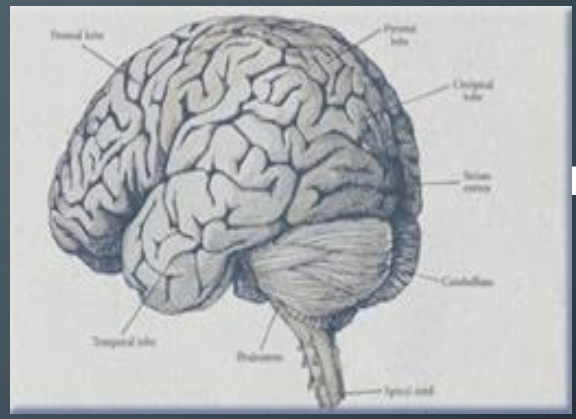
# FUSION OF FUNCTIONAL RESULTS AND ANATOMICAL IMAGE

- Use co-register to overlay onto a subject's own anatomical scan
- SPM has option to overlay onto standard brain in MNI space



# WHAT DO WE DO WITH THIS "ACTIVATION INFORMATION"?

- Whole brain analysis
  - Explore areas throughout that are active
  - Compare subjects or groups

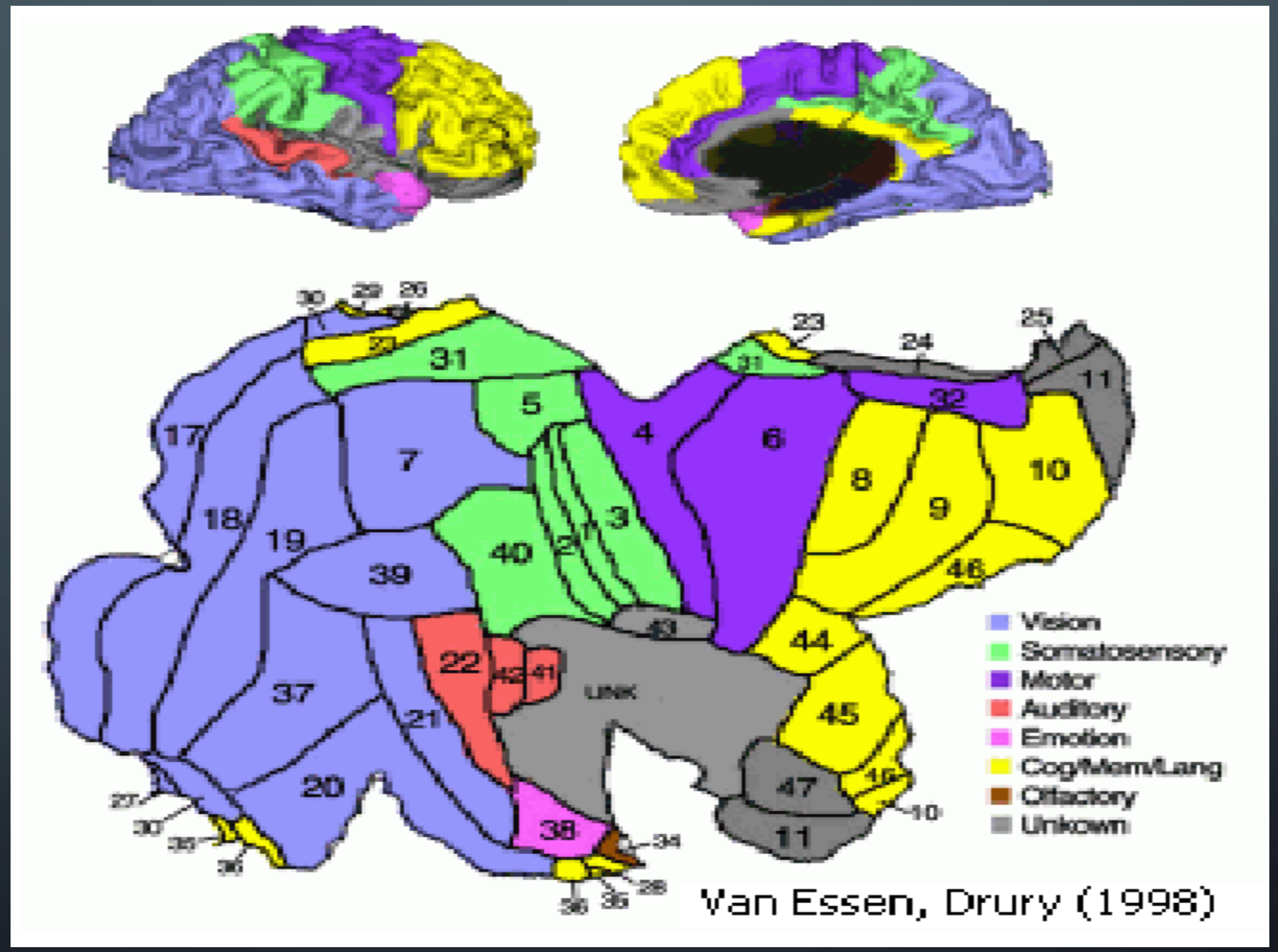


n

- Region of interest (ROI) analysis
  - Explore specific areas of interest in the brain
  - Percent activation in the area –

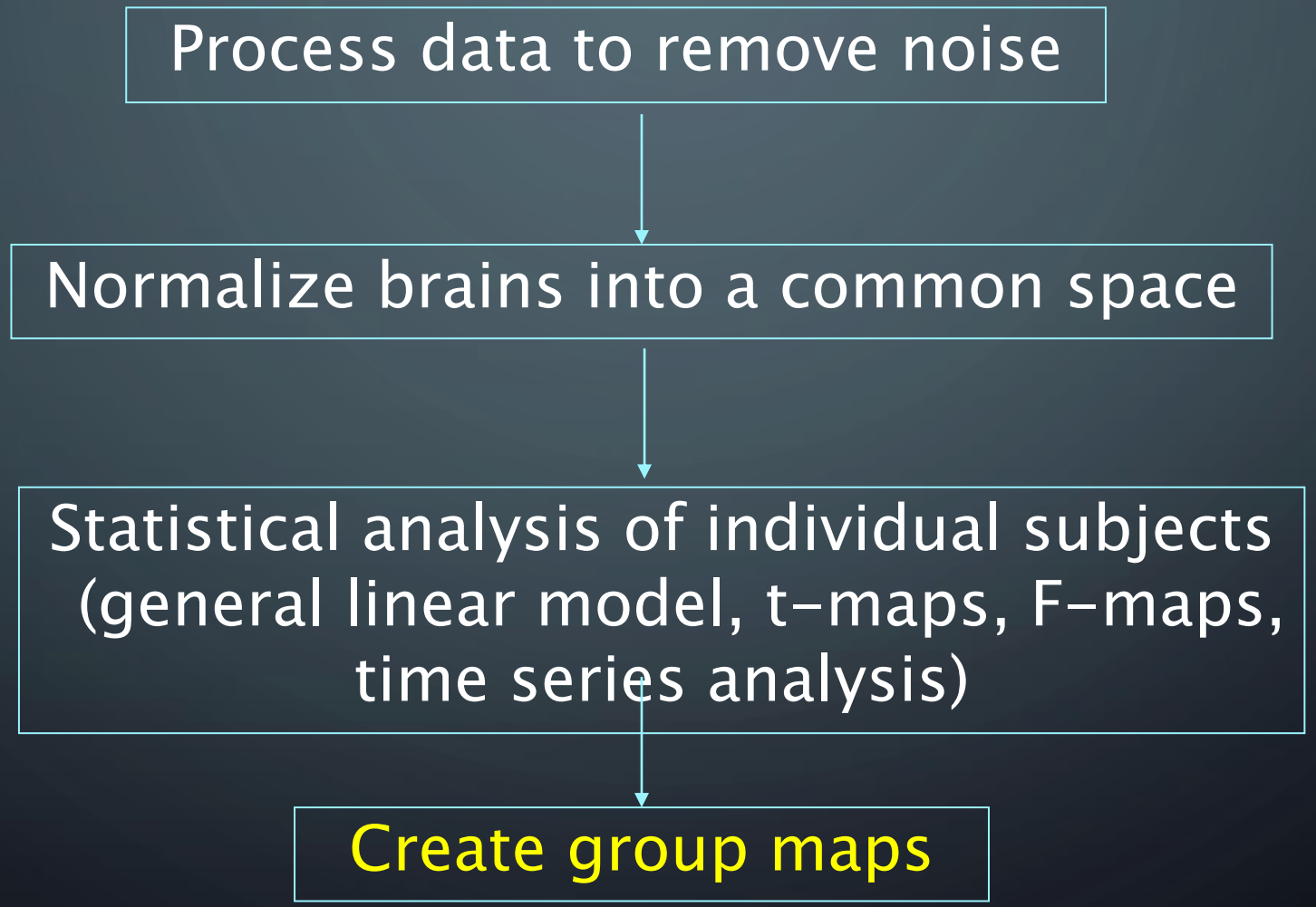
    (number of active voxels/total number of voxels)
  - Explore "level of activation" as a function of another variable (example, IQ)

# Region of Interest Analysis




Map of Brodmann's Areas

# EXAMPLE OF FMRI DATA ANALYSIS STEPS



# PROBLEMS OF GROUP MAPS

1. Limited number of subjects

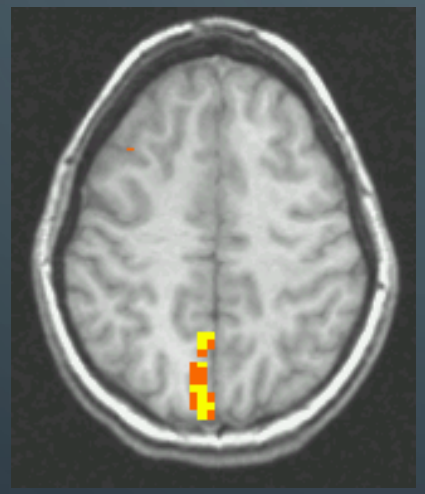
2. All brains must be “warped” into a normalized space

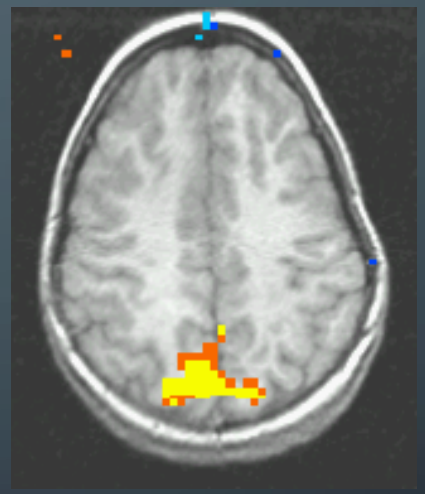
3. Need a method for “pooling” statistical data

4. Levels of activation vary across subjects

# FMRI GROUP ANALYSIS

- Can look at activation for a single subject
- Can compare between 2 subjects





- What if we want to compare between 2 groups of subjects?
- Need more subjects for statistical power

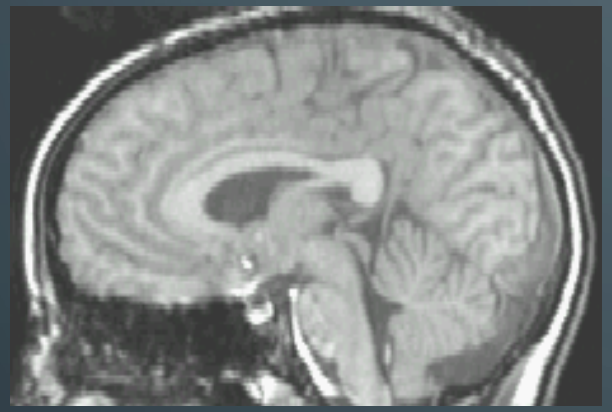
# BRAIN NORMALIZATION

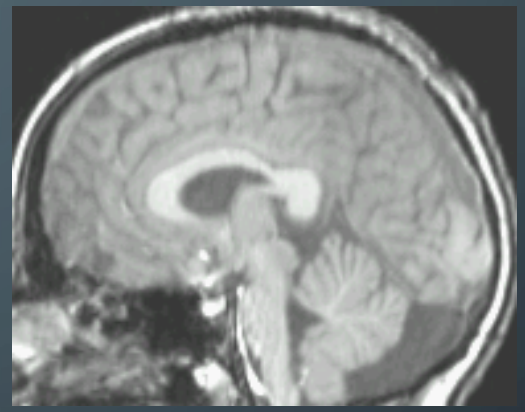
- Warp all brains into a “normalized” space by lining up brain landmarks
- Talairach and Tournoux Atlas, Montreal Neurological Institute (MNI) template
- Although this is a standard procedure in fMRI group analysis, it introduces *spatial smoothing and other errors*

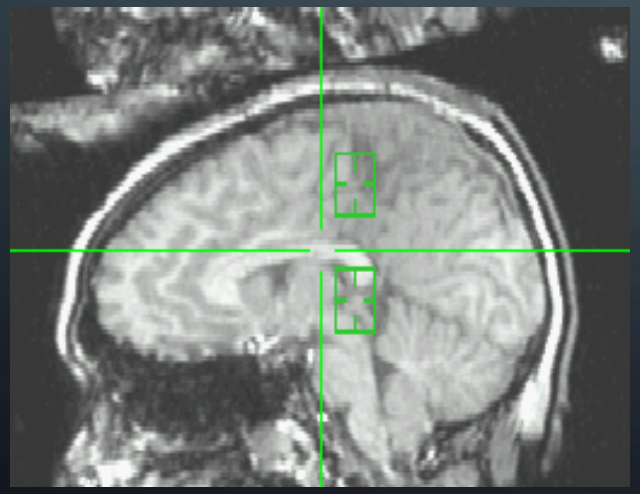
# “TALAIRACHING” OF BRAINS

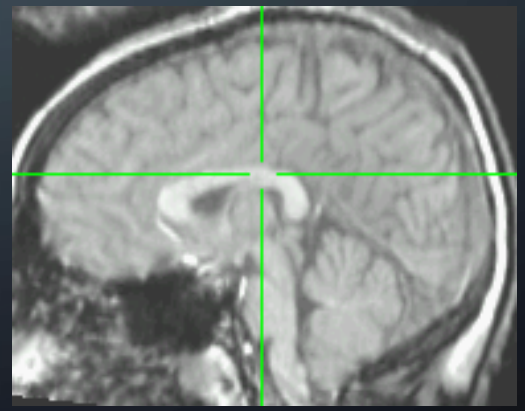
BEFORE

AFTER

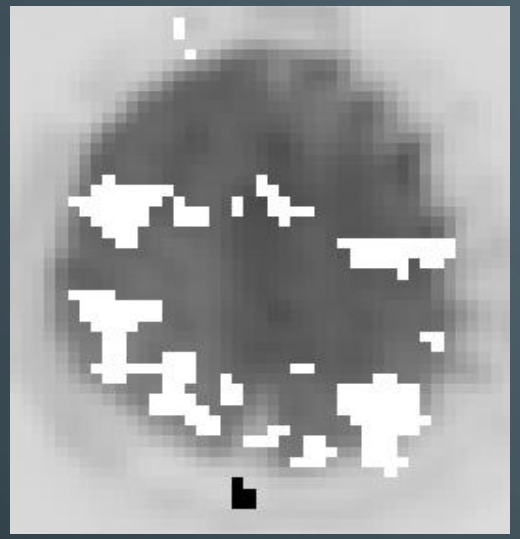




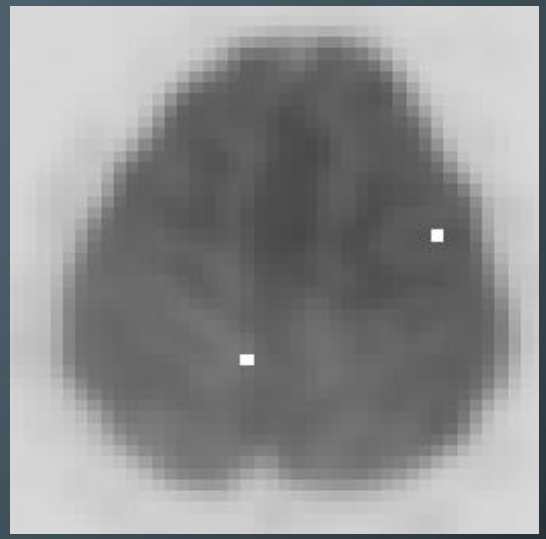


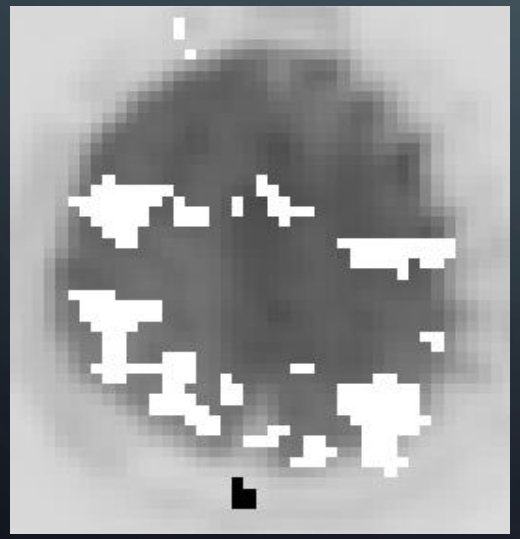


# EXAMPLE OF VARIATIONS IN ACTIVATION

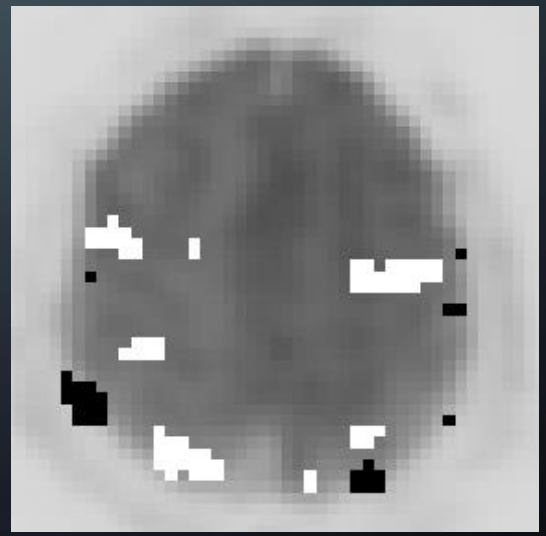


Same Task
Different Subjects





Same Subject
Same Task
Different Years



# HOW DO WE COMBINE STATISTICAL INFORMATION?

- Individual subject results are already based on statistical processing
- Combining Tests (T values, P values)
  - *Fisher's Method (1950)*
  - *Tippett's Method (1931)*
  - *The Stouffer Method (1949)*
  - *Averaging T-maps*
  - *Worsley and Friston (2000)*
- Combined estimation or "meta-analysis"
  - *Fixed effects and random effects models*

# COMBINING METHODS

*For k independent tests of a particular null hypothesis, with corresponding P and T values…*

Fisher's Method

$$T_F = -2\sum_{i=1}^{k} \log P_i$$

Stouffer Method

$$T_s = \sum_{i=1}^{k} \frac{\Phi^{-1}(1-P_i)}{\sqrt{k}}$$

Averaging T-maps

$$T_A = \sum_{i=1}^{k} \frac{T_i}{\sqrt{k}}$$

The Random Effects Model

$$y_i = (\theta + e_i) + \varepsilon_i$$

$$\hat{\theta}^* = \frac{\sum_{i=1}^{k} w_i^* y_i}{\sum_{i=1}^{k} w_i^*}$$

$$w_i^* = \frac{1}{(s_i^2 + \hat{\sigma}_\theta^2)}$$

# WHICH METHODS ARE “BEST”?

- For robust results without excessive information smoothing –
  - *Fixed or Random effects*
  - *The Stouffer Method*
  - *Fisher’s Method*
- How sensitive are these to the effects of individual subjects?

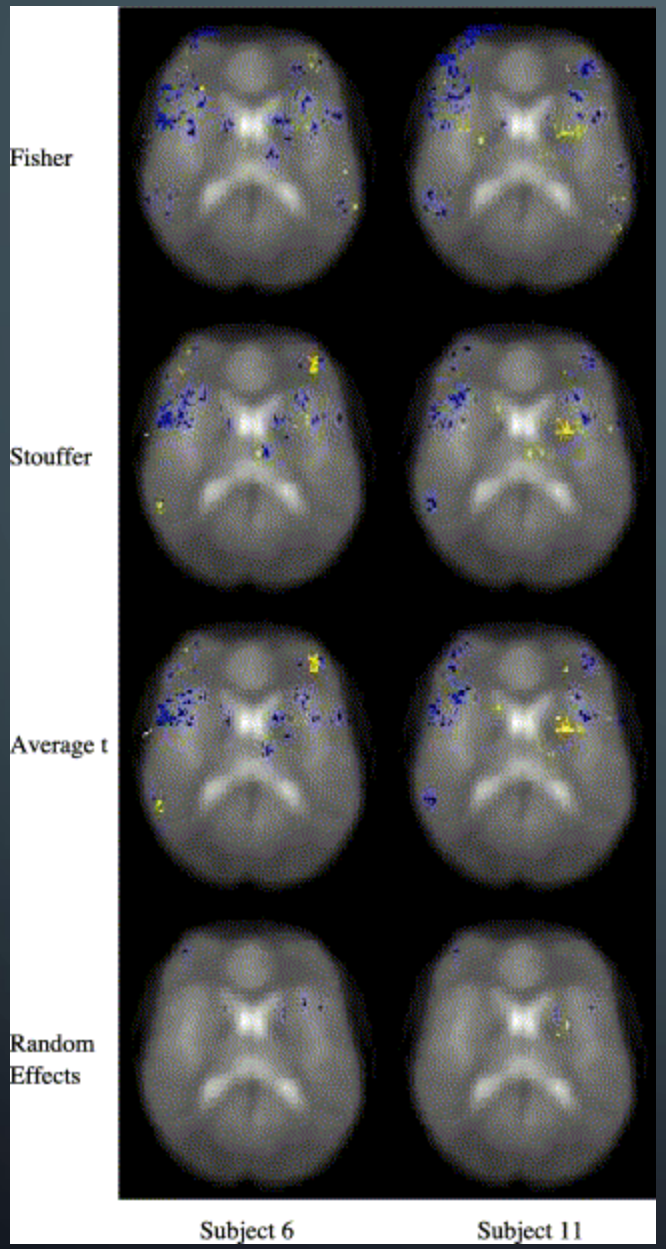
# SENSITIVITY ASSESSMENT OF GROUP MAPS

- 4 combining methods, 11 subjects
- Used “delete one subject diagnostics” (jack-knifing) to create “leave one out” maps
- Recomputed group maps
- Examined changes in the resulting maps for each method as each subject was left out

# DISPARITY MEASURES FOR "LEAVE ONE OUT" MAPS

Using a standard threshold, compared each "leave one out" map to the complete group map (CGM), examining:

- Enhancing voxels – *# voxels added to CGM*
- Diminishing voxels - *# voxels removed from CGM*
- Relative effect – *(# enhancing voxels + # diminishing voxels) / # voxels in CGM*
- Percent overlap – *# voxels in the subject's individual t-map also present in CGM*

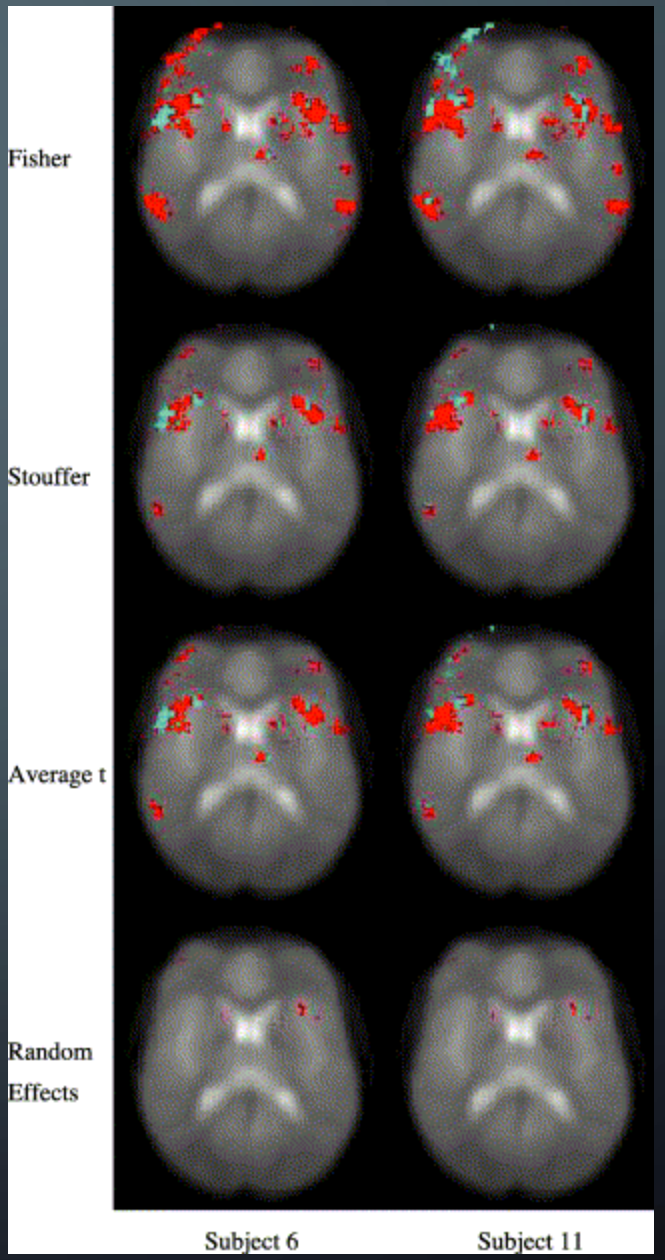



Enhancing

Diminishing

Active in CGM

Overlapping




Difference Maps

Overlap Maps

# DISPARITY TABLES

| Study | Enhancing voxels | Diminishing voxels | Relative effect | Percent overlap |
|---|---|---|---|---|
| 1 | 319 | 9 | 0.47 | 0.2741 |
| 2 | 170 | 62 | 0.34 | 0.0539 |
| 3 | 86 | 190 | 0.40 | 0.0233 |
| 4 | 185 | 47 | 0.34 | 0.1108 |
| 5 | 155 | 29 | 0.27 | 0 |
| 6 | 266 | 55 | 0.47 | 0.2230 |
| 7 | 64 | 175 | 0.35 | 0.0029 |
| 8 | 249 | 51 | 0.44 | 0.2784 |
| 9 | 132 | 93 | 0.33 | 0.0204 |
| 10 | 199 | 76 | 0.40 | 0.1005 |
| 11 | 205 | 89 | 0.43 | 0.1589 |
| Mean | 184.55 | 79.64 | 0.39 | 0.11 |
| SD | 75.88 | 56.49 | 0.06 | 0.11 |

Results from the Stouffer Method

## Fisher

| Study | Enhancing voxels | Diminishing voxels | Relative effect | Percent overlap |
|---|---|---|---|---|
| 1 | 432 | 50 | 0.30 | 0.1857 |
| 2 | 176 | 113 | 0.18 | 0.0414 |
| 3 | 83 | 169 | 0.16 | 0.0113 |
| 4 | 307 | 56 | 0.23 | 0.0909 |
| 5 | 140 | 106 | 0.15 | 0.0038 |
| 6 | 363 | 42 | 0.25 | 0.1242 |
| 7 | 82 | 134 | 0.13 | 0.0050 |
| 8 | 673 | 14 | 0.43 | 0.3683 |
| 9 | 156 | 146 | 0.19 | 0.0176 |
| 10 | 254 | 106 | 0.23 | 0.0928 |
| 11 | 399 | 75 | 0.30 | 0.2114 |
| Mean | 278.64 | 91.91 | 0.23 | 0.10 |
| SD | 179.94 | 48.35 | 0.09 | 0.11 |

## Random Effects

| Study | Enhancing voxels | Diminishing voxels | Relative effect | Percent overlap |
|---|---|---|---|---|
| 1 | 10 | 8 | 0.60 | 0.0333 |
| 2 | 13 | 2 | 0.50 | 0 |
| 3 | 6 | 42 | 1.60 | 0 |
| 4 | 20 | 2 | 0.73 | 0.1000 |
| 5 | 18 | 2 | 0.67 | 0 |
| 6 | 18 | 1 | 0.63 | 0 |
| 7 | 7 | 17 | 0.80 | 0 |
| 8 | 14 | 6 | 0.67 | 0.0333 |
| 9 | 9 | 3 | 0.40 | 0 |
| 10 | 11 | 5 | 0.53 | 0.0333 |
| 11 | 8 | 16 | 0.80 | 0.0333 |
| Mean | 12.18 | 9.45 | 0.72 | 0.02 |
| SD | 4.81 | 12.14 | 0.32 | 0.03 |

# RESULTS AND CONCLUSIONS


- Fisher's Method – *exploratory studies*
- The Stouffer method/ Averaging of T-maps – *general use*
- Random effects – *large subject groups*



*McNamee and Lazar (2004) "Assessing the Sensitivity of fMRI Group Maps" NeuroImage, 22: 920-931.*