FMRI Experimental Design

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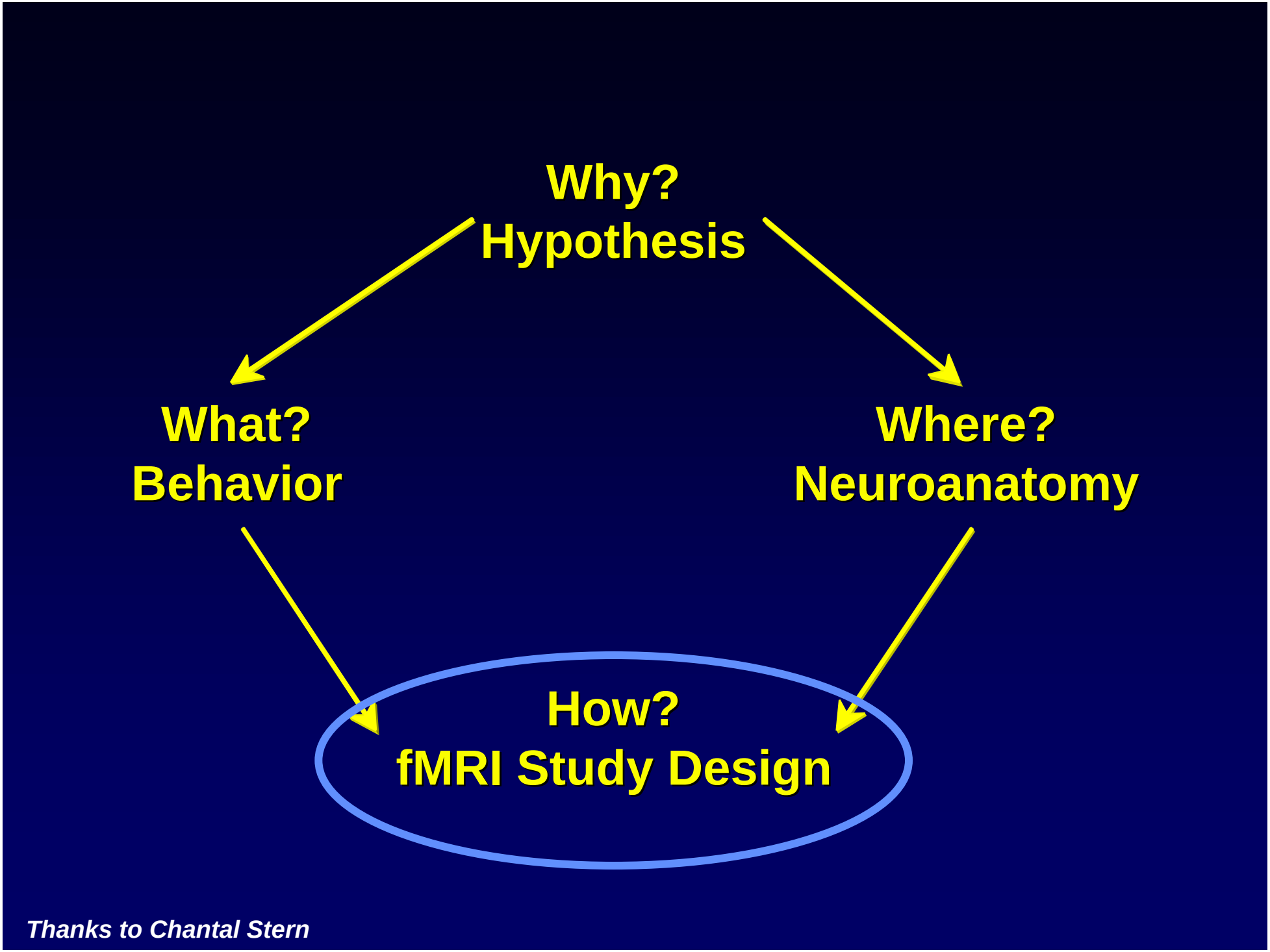
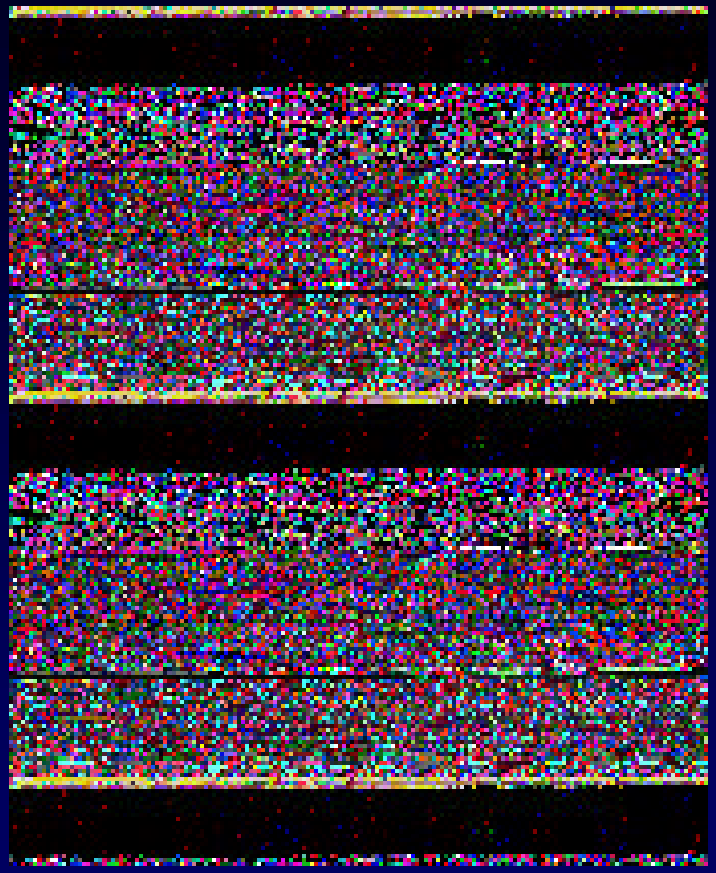
Because fMRI BOLD data is not an absolute measure of neuronal activity, all study designs must provide the opportunity to statistically contrast the neuronal activity of interest with a suitable rest or background condition.

Thus, study design is of paramount importance.



Thanks to Chantal Stern

43 * 7 = ?



Key Points

- What can fMRI tell you?
- Always comparing across conditions
- Characteristics of the hemodynamic response (HRF) and how this affected the sequential development of fMRI paradigms and influences study design
- Sense of important design issues

What (good) is fMRI?

What it can tell you:

- Relative local “neural” activity (LFP’s ?)
- NOT absolute neural activity
- NOT excitation vs inhibition
- NOT about necessity of a given region for a task
- NOT fine-grained temporal information

Key Points

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Subtraction Paradigm

Donder's method:

Ex: How to measure time of a mental transformation?

A random series of A's and B's presented and the subject must:

1. Respond whenever an event occurs (RTi)
2. Respond only to A not to B (RTii)
3. Respond X to A and Y to B (RTiii)

RTi = RT(detect) + RT(response)

RTii = RT(detect) + RT(discrimination) + RT(response)

RTiii = RT(detect) + RT(discrimination) + RT(choice) + RT(response)

THUS, RT(discrimination) = RTii - RTi

RT(choice) = RTiii - RTii

Criticisms of Subtraction Paradigm

1. That we already know what 'counts' as a single mental process (i.e. choice is a single mental process?)

2. Assume that adding components does not affect other processes (i.e. assumption of pure insertion)

THUS, one should pick tasks that differ along ONE dimension (either change the task OR the stimuli but not BOTH!)

And a resting baseline is good to include, however, the interpretation should be taken lightly…(more later)

The loose task comparison

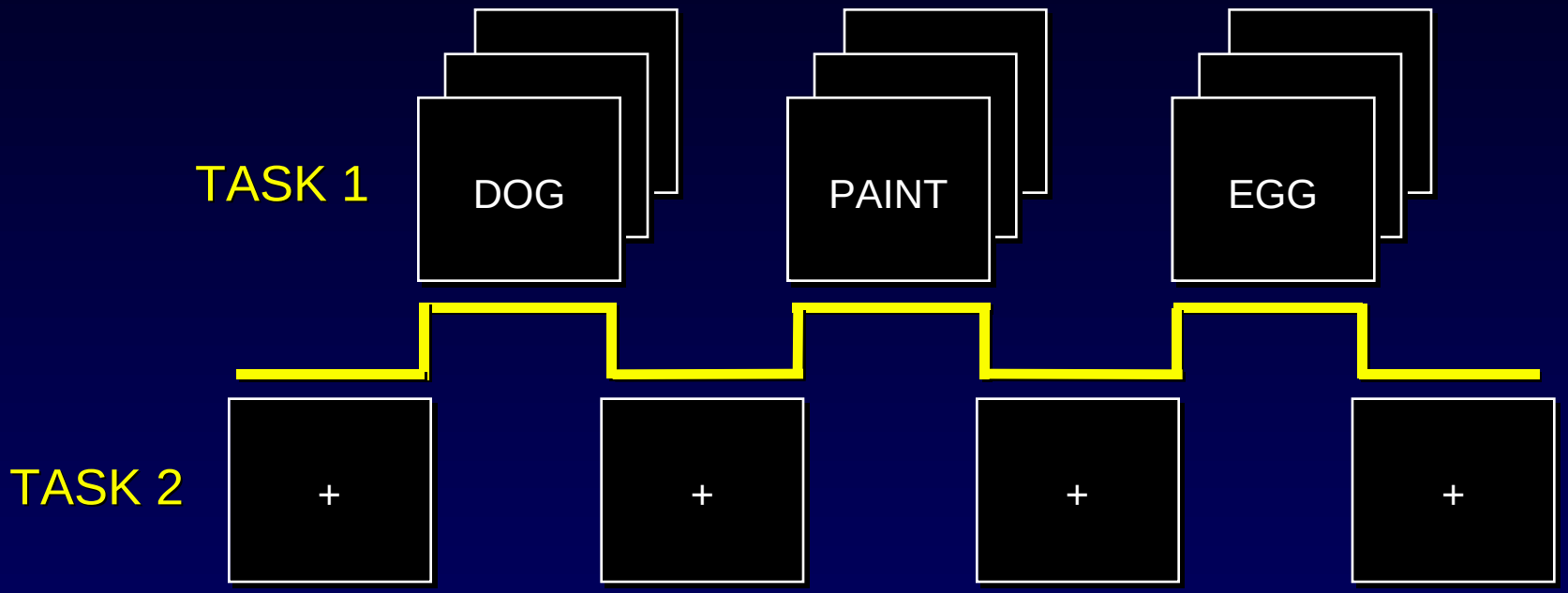
Does not hold all variables constant BUT:

(1) Uses a low level reference task

(2) Allows the data to be examined for predictable stimulus or response driven activations

(3) Allows the more extensive activation pattern to be observed

The “loose” Task Comparison

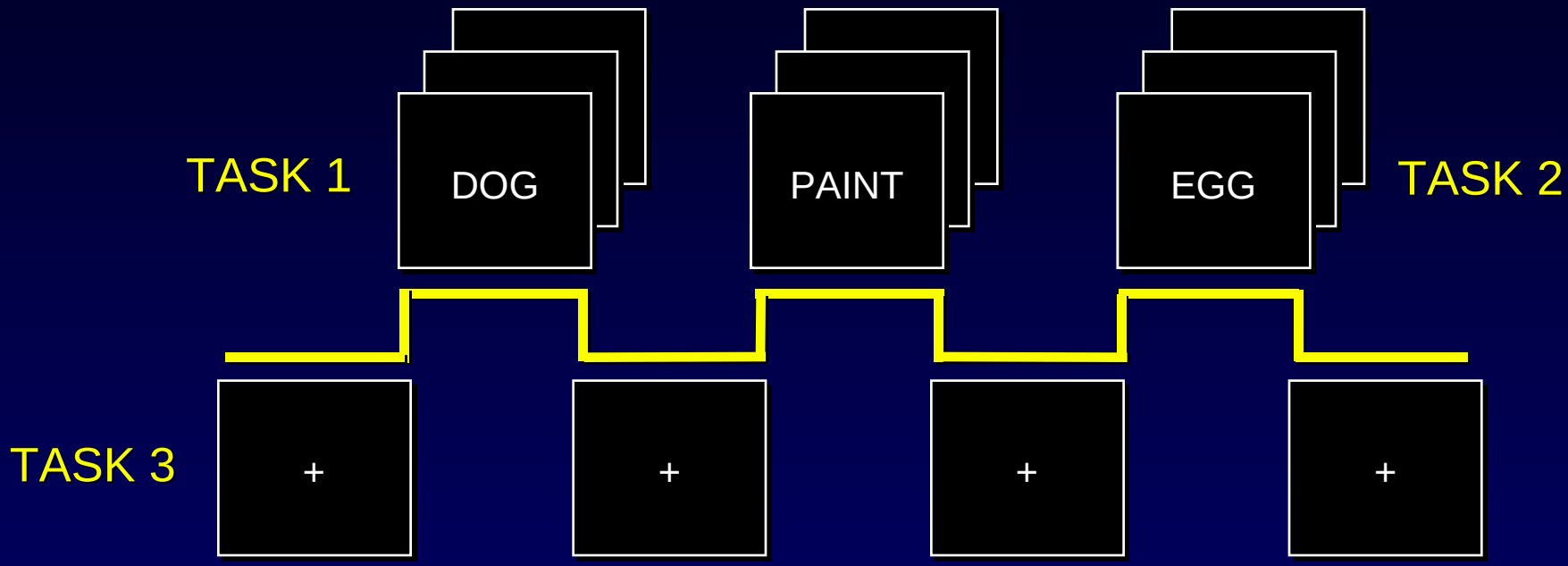


The tight task comparison

Try to hold all variables constant including:

- **Stimulus display (nominally or statistically)**
- **Response and response selection characteristics**
- **Performance level- especially if comparing cohorts**
- **Eye movements**
- **Emotional state (minimize anxiety and boredom)**

The “tight” Task Comparison



BRAIN AREAS THAT DIFFER

TASK 1 TASK 2 2 minus 1

ALL ACTIVE BRAIN AREAS

Thanks to Randy Buckner

Example...

Interested in semantic processing and how it affects memory...

Parameters to specify in any experiment

1. Subjects: normal vs special populations

2. What part of brain look at? How many slices can you have for your TR?

3. Choosing your TR: How often can you take a full set of pictures

4. What coil will you use?
    surface coils: higher SNR, only partial coverage
    head coils: lower SNR, complete coverage

5. Toggle many times between conditions within a scan

6. Run as many scans as possible within a subject

Key Points

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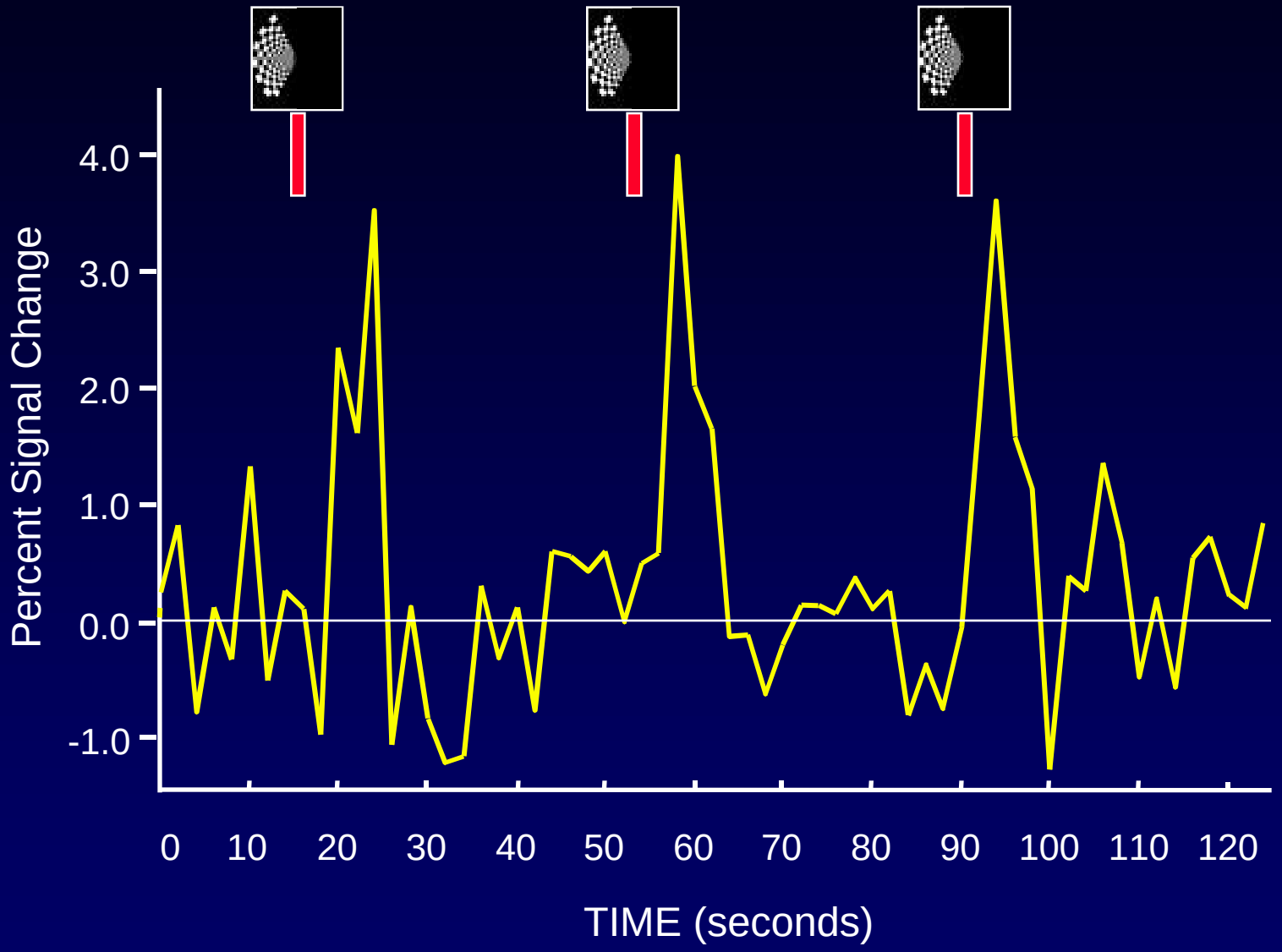
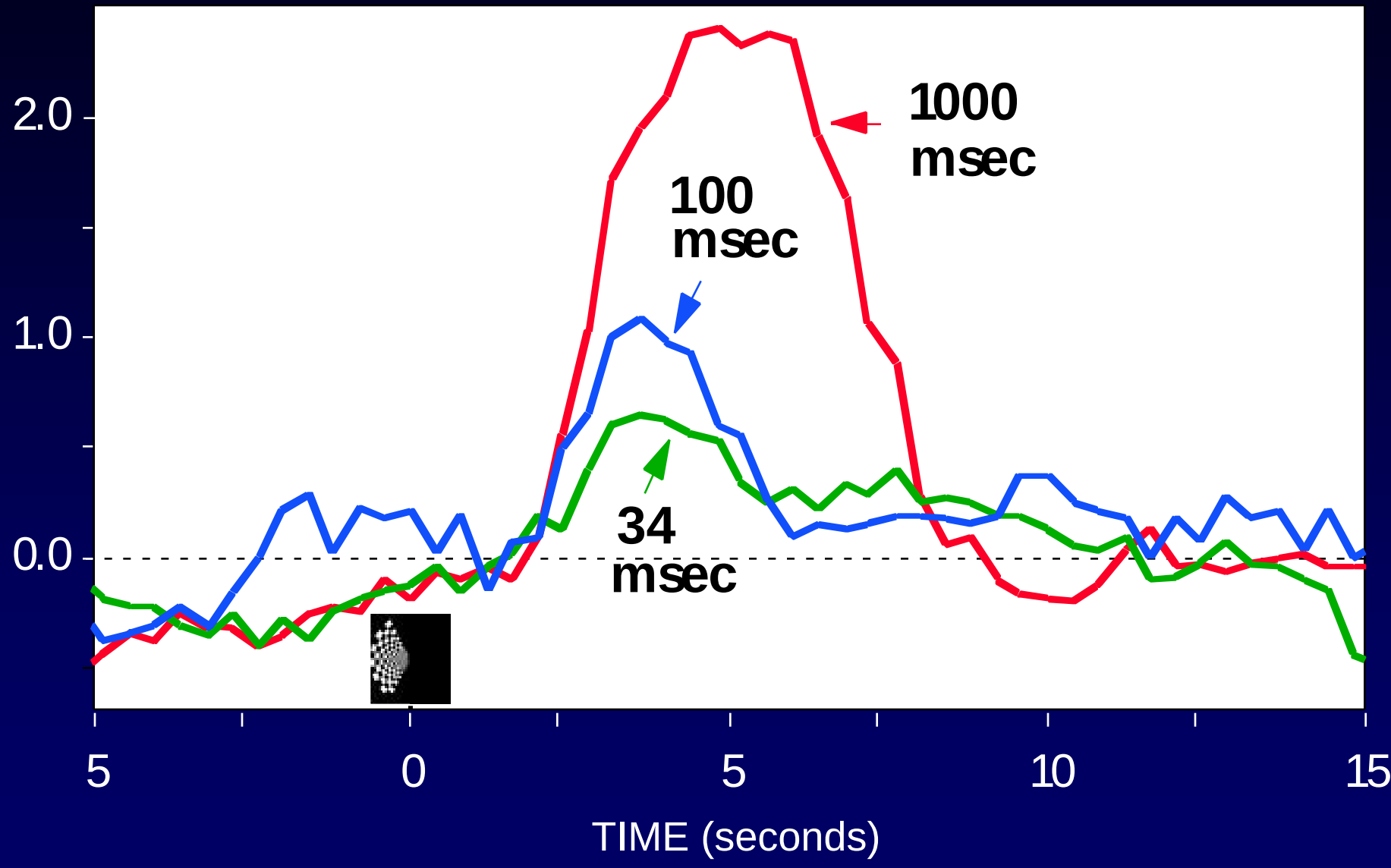
Visual Stimulation - 2 sec Flashes



[Blamire, Ogawa et al., ***PNAS***, 1992]

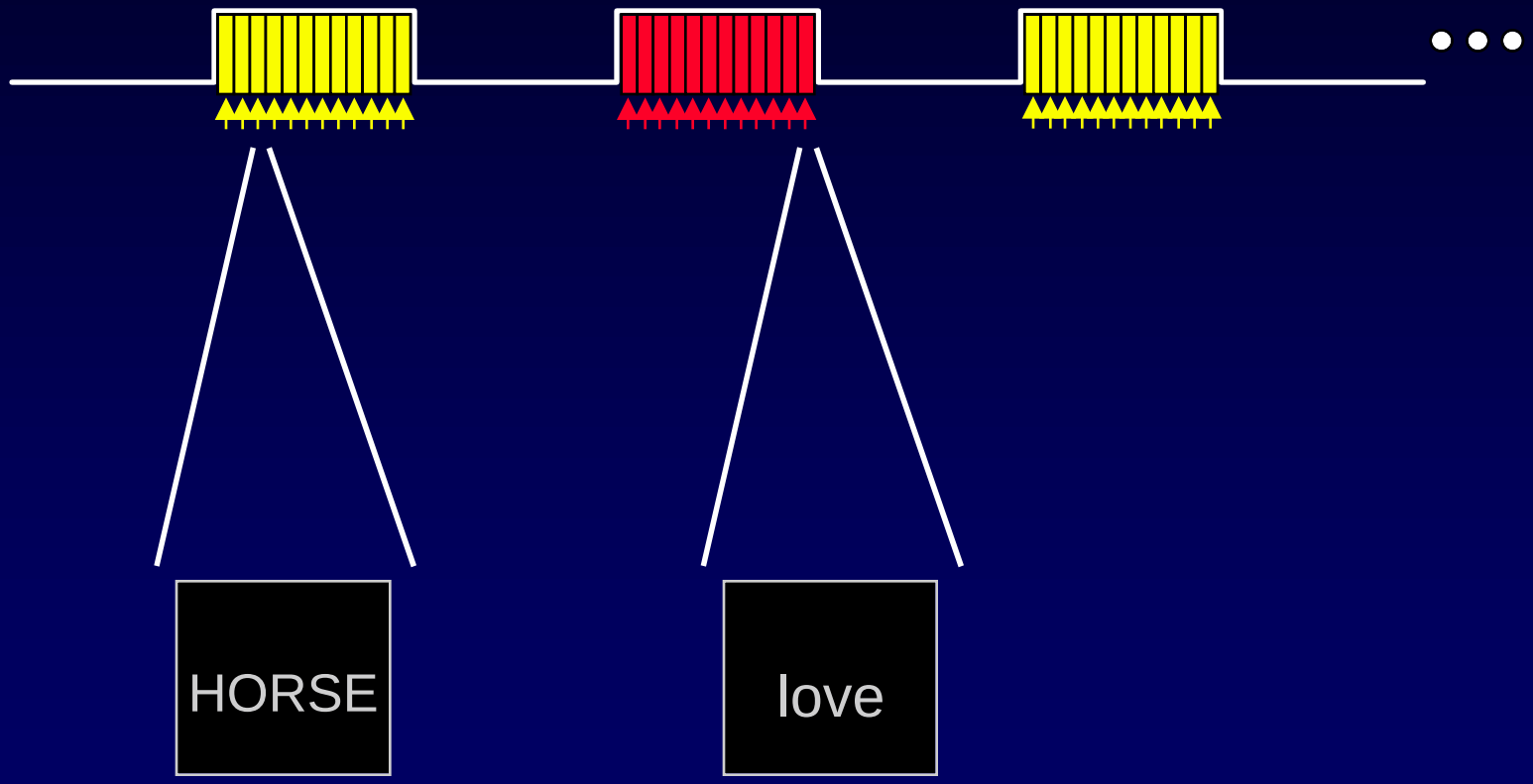
Visual Cortex During Brief Visual Stimulation



[Courtesy of Robert Savoy, Kathleen O'Craven MGH-NMR Center]

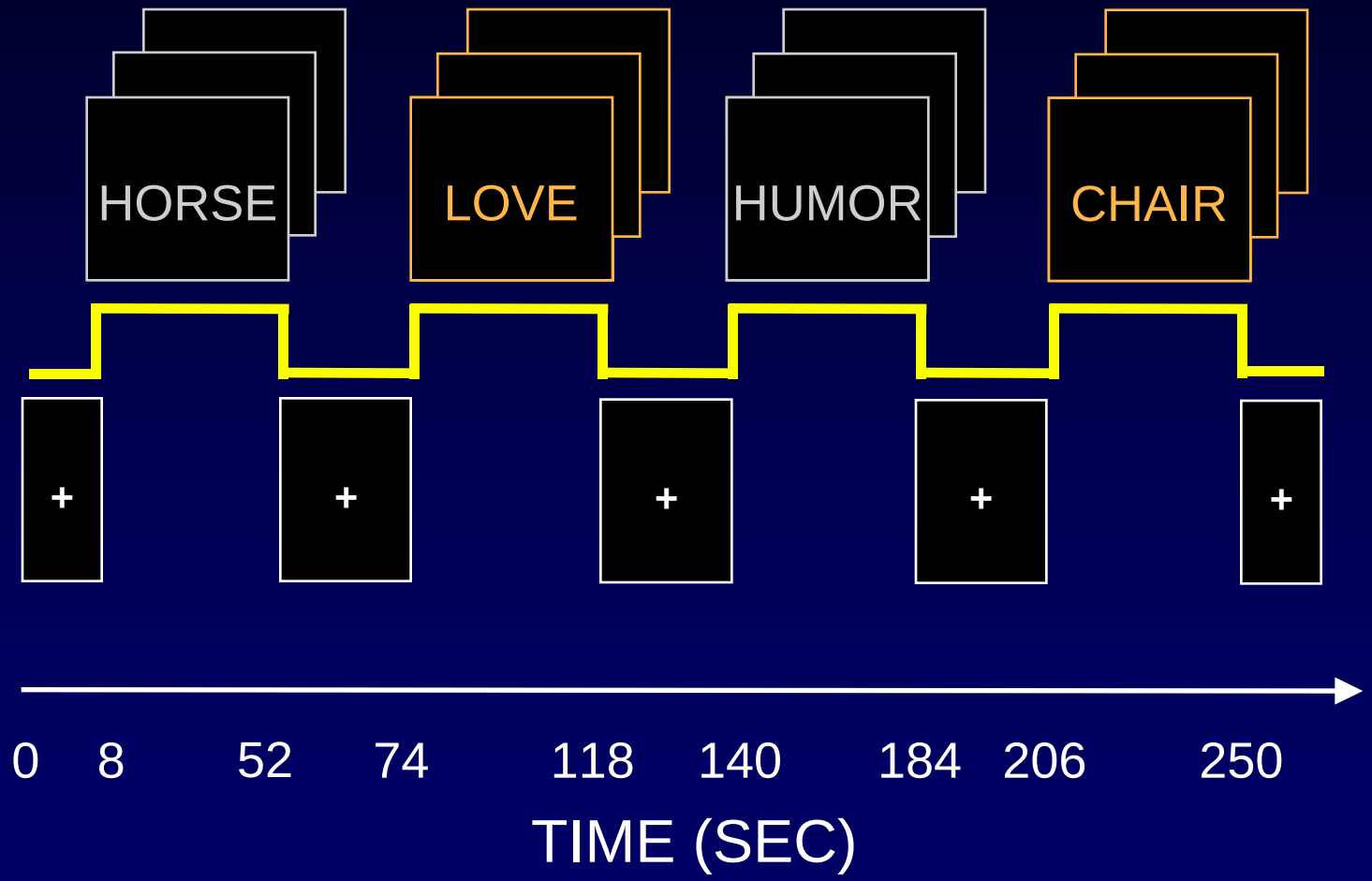
Blocked design fMRI

BLOCKED:



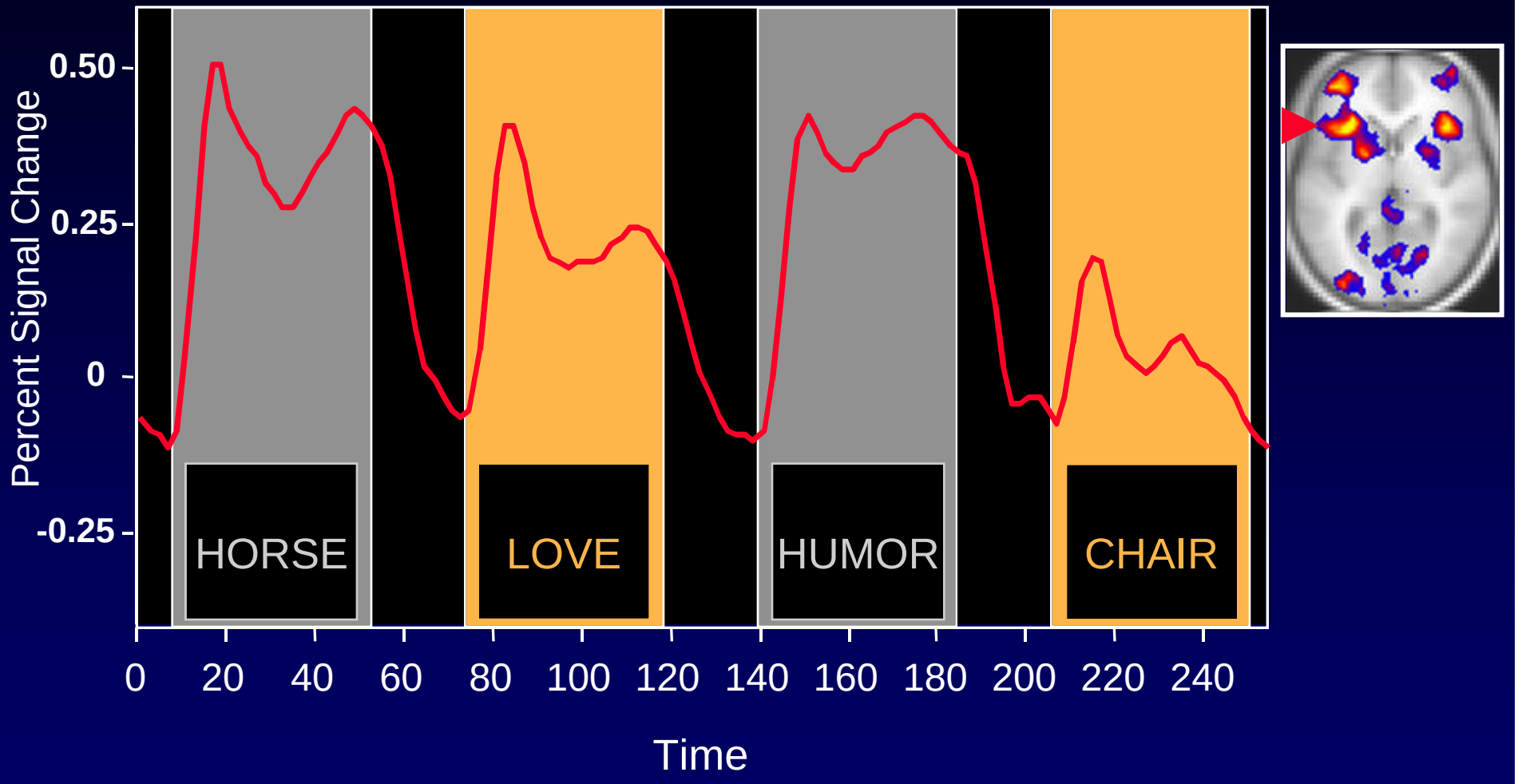
(abstract or concrete?) (upper or lowercase?)

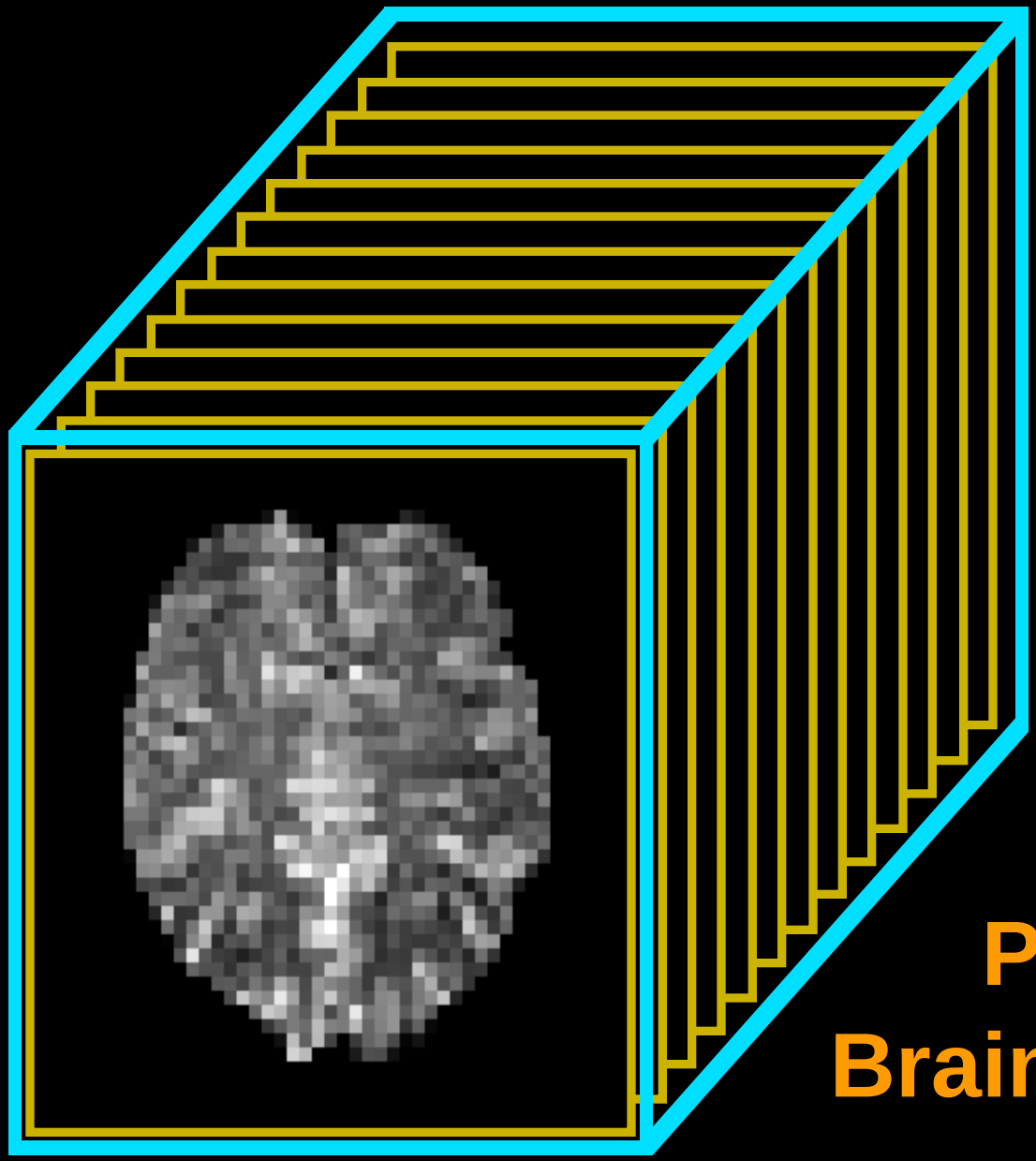
“Blocked” fMRI: Memory Paradigm



[Wagner et al., ***OHBM***, 1998]

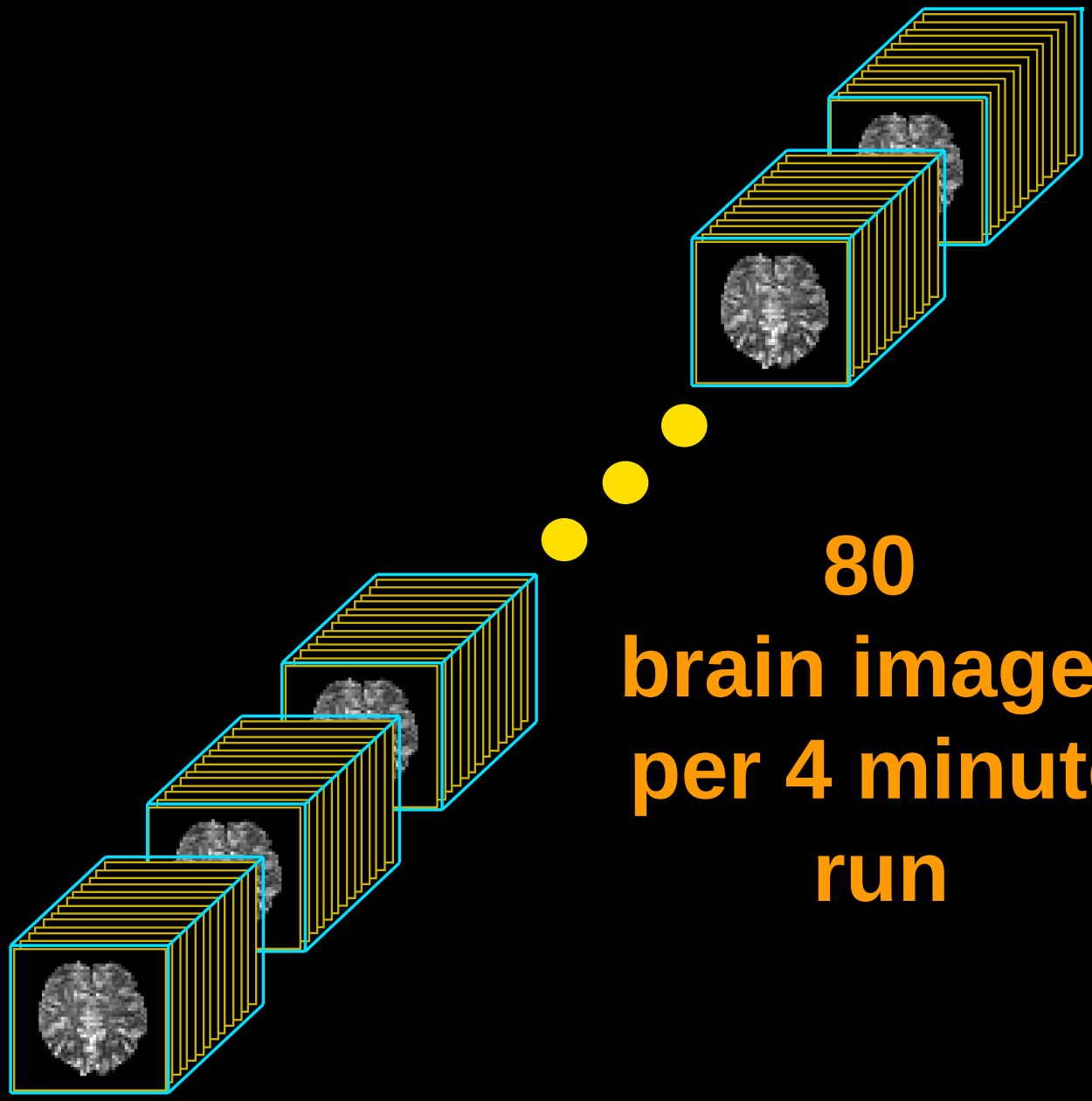
Typical Blocked-Design Response





13 Slices Per Brain Image

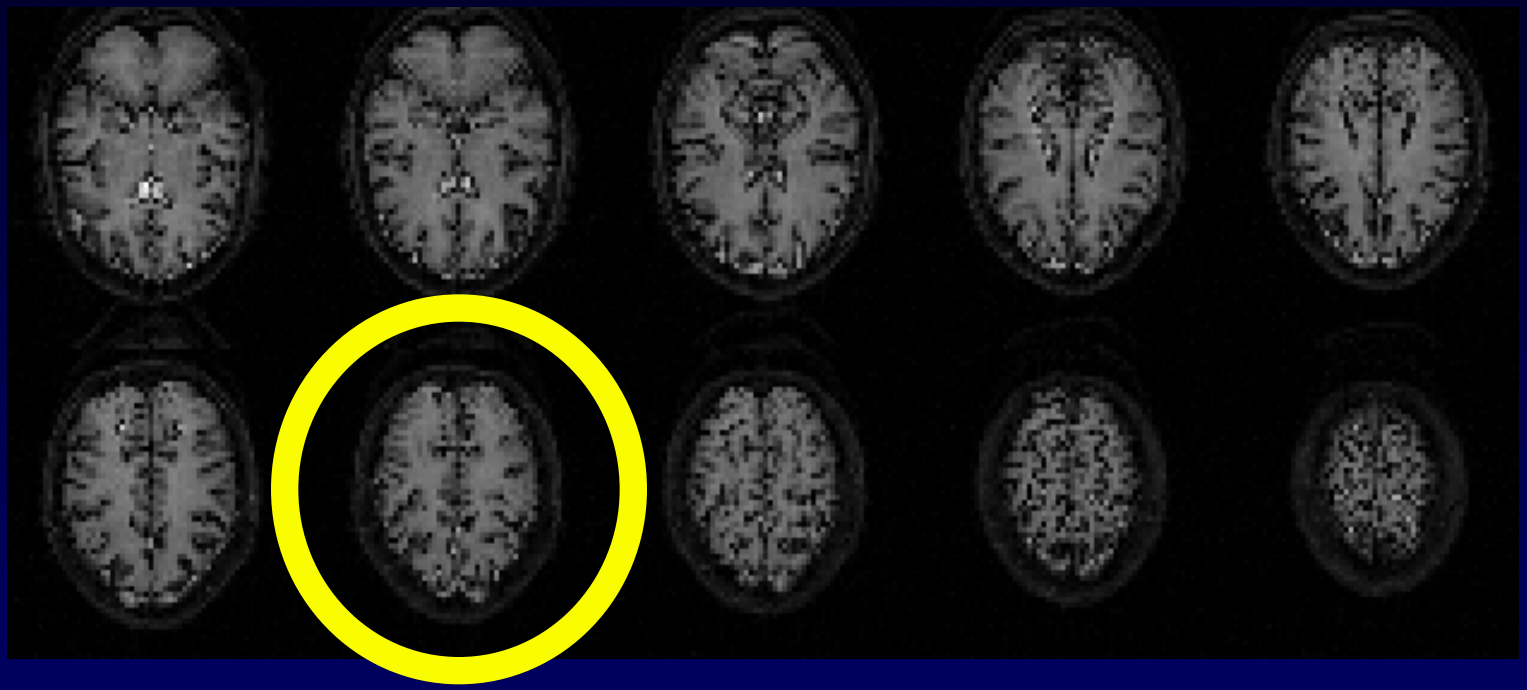
Thanks to Robert Savoy



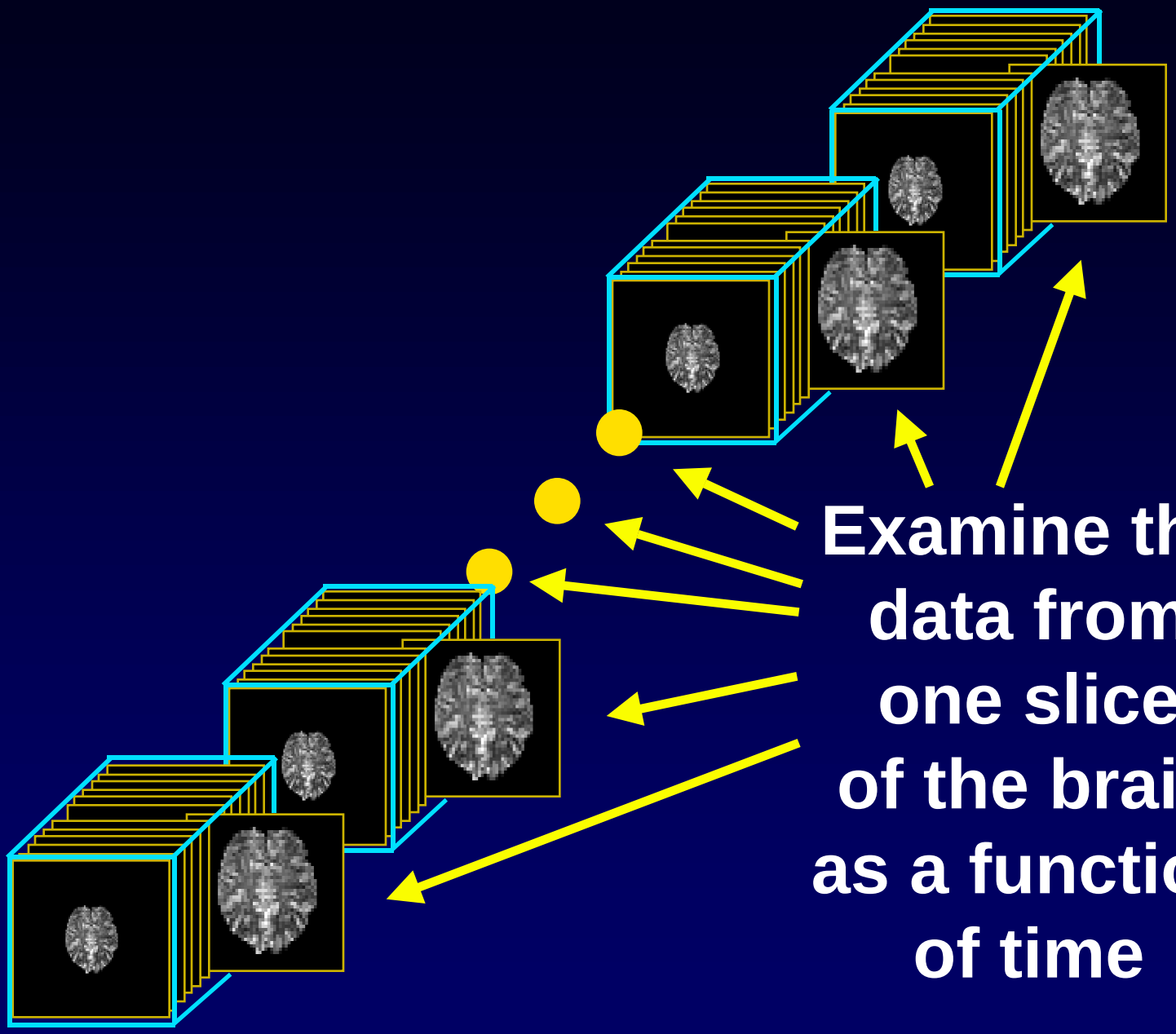
80 brain images per 4 minute run

Thanks to Robert Savoy

For purposes of illustration…….

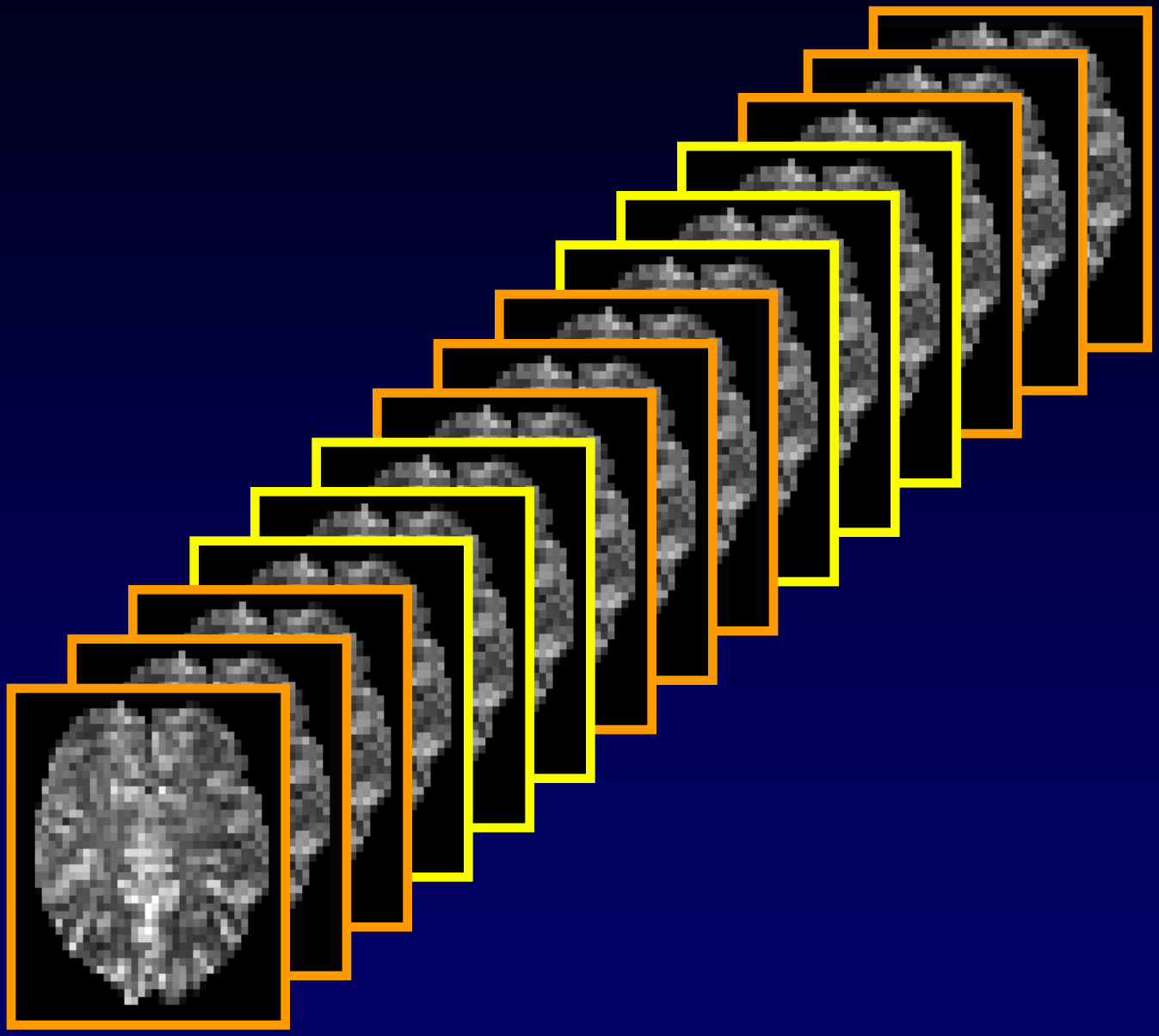


Thanks to Robert Savoy

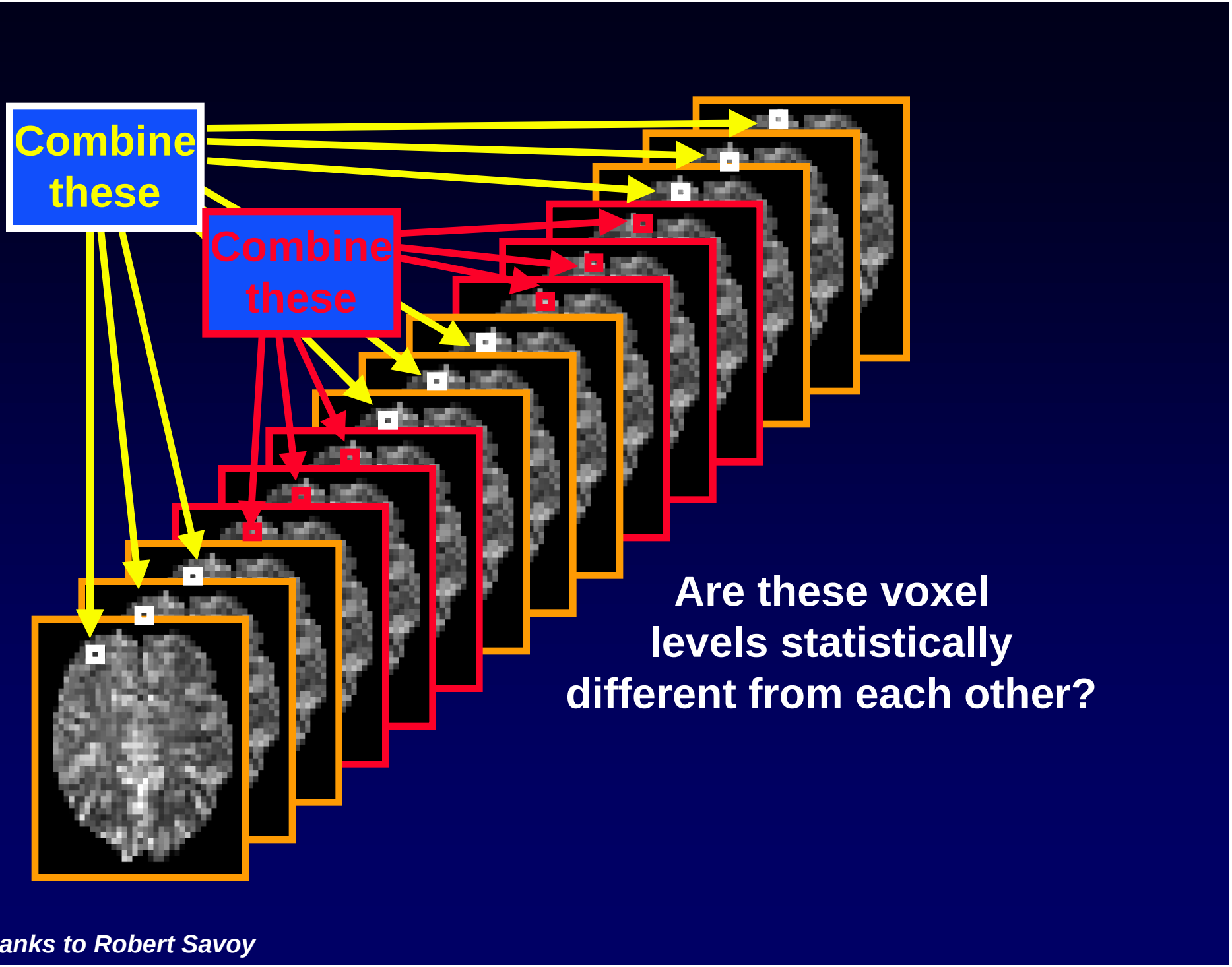


Examine the data from one slice of the brain as a function of time

Thanks to Robert Savoy



Thanks to Robert Savoy



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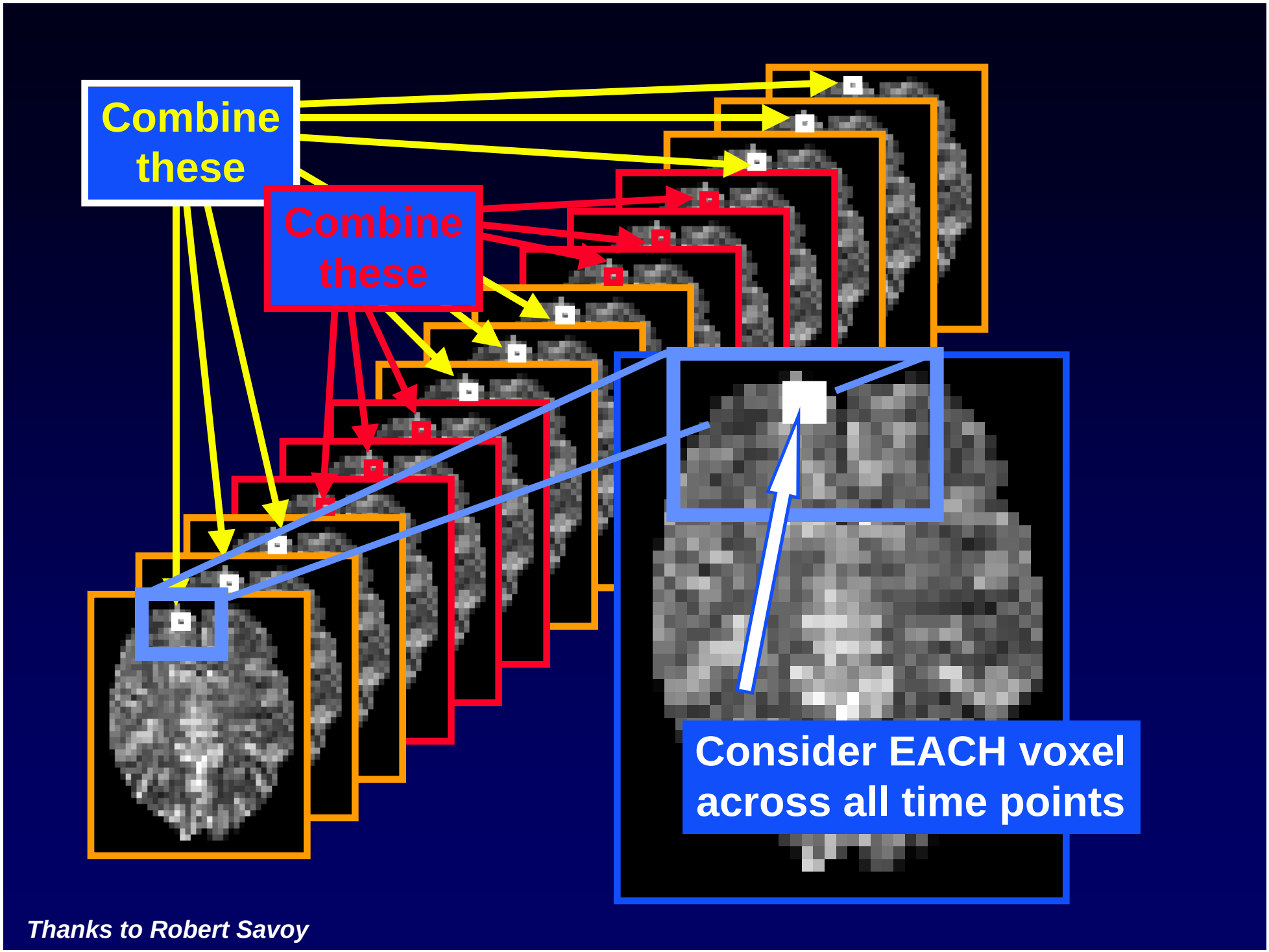

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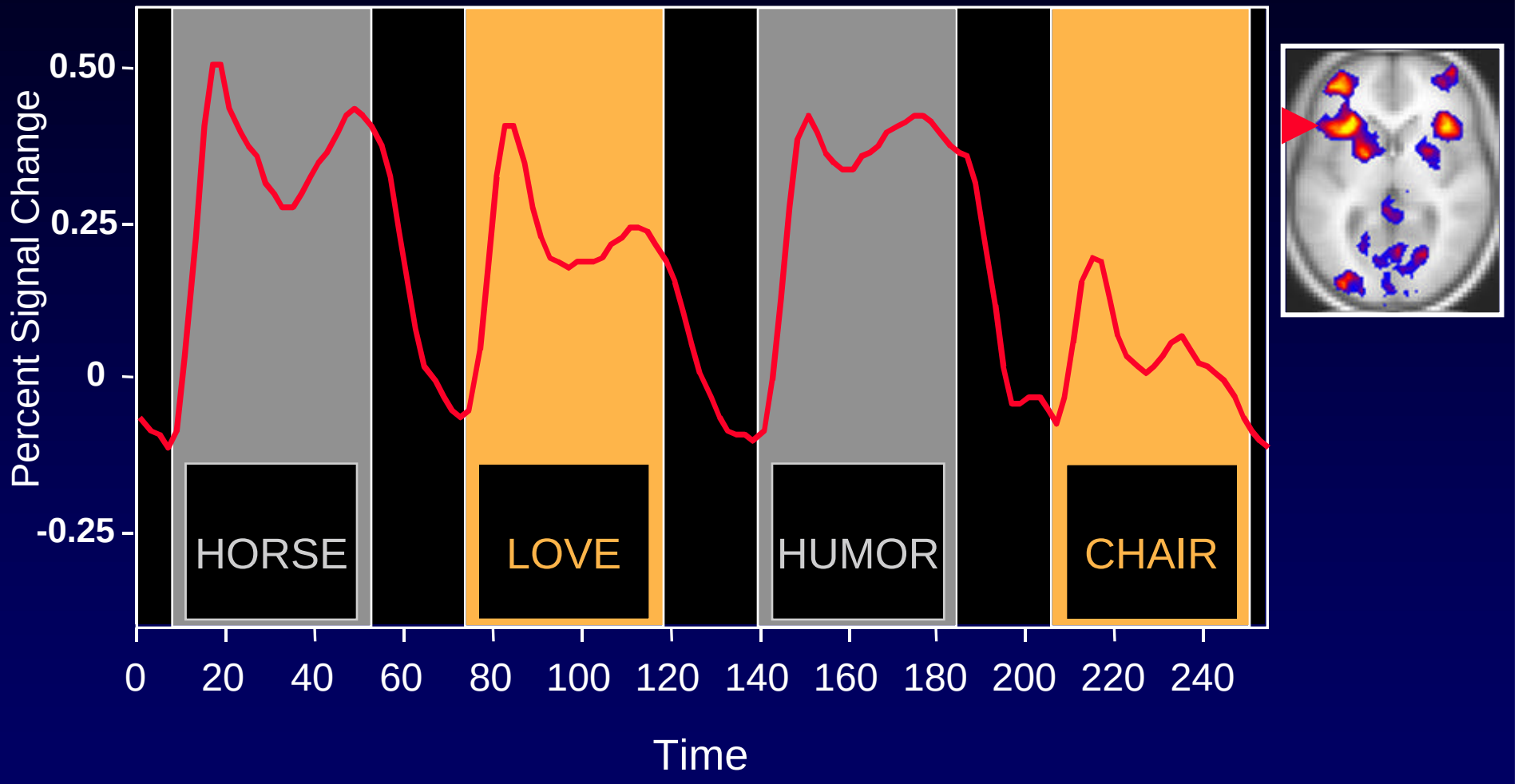
Typical Blocked-Design Response



Event-Related fMRI

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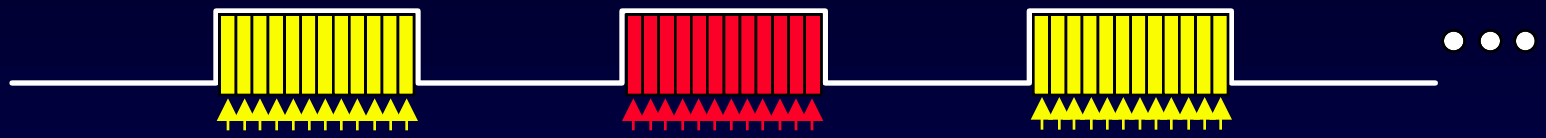
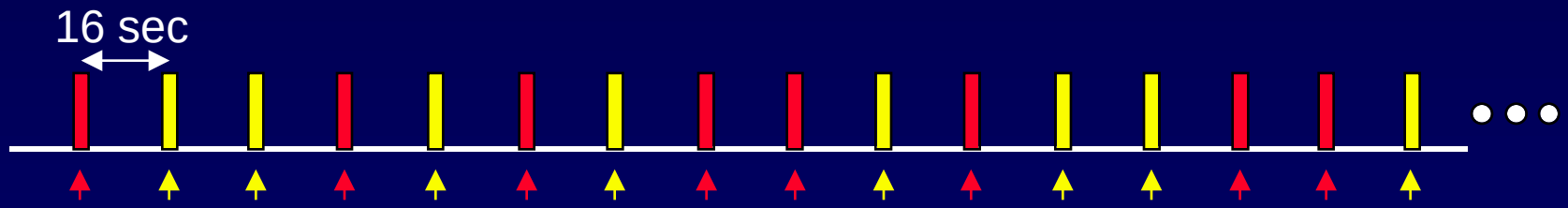
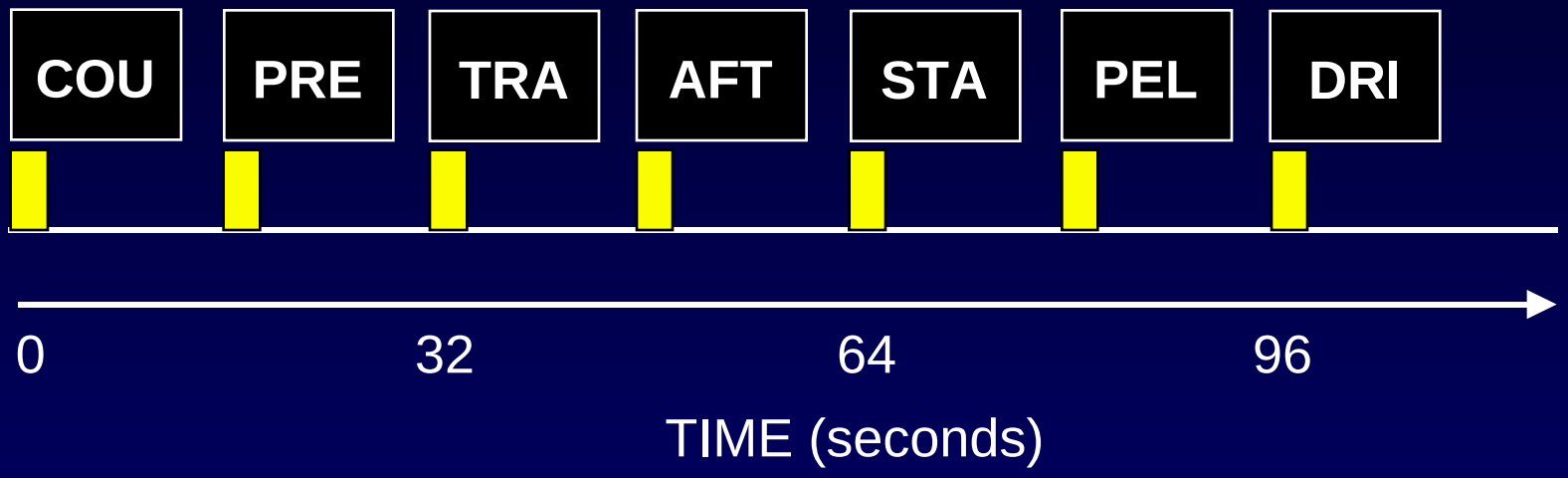


SPACED EVENT-RELATED:

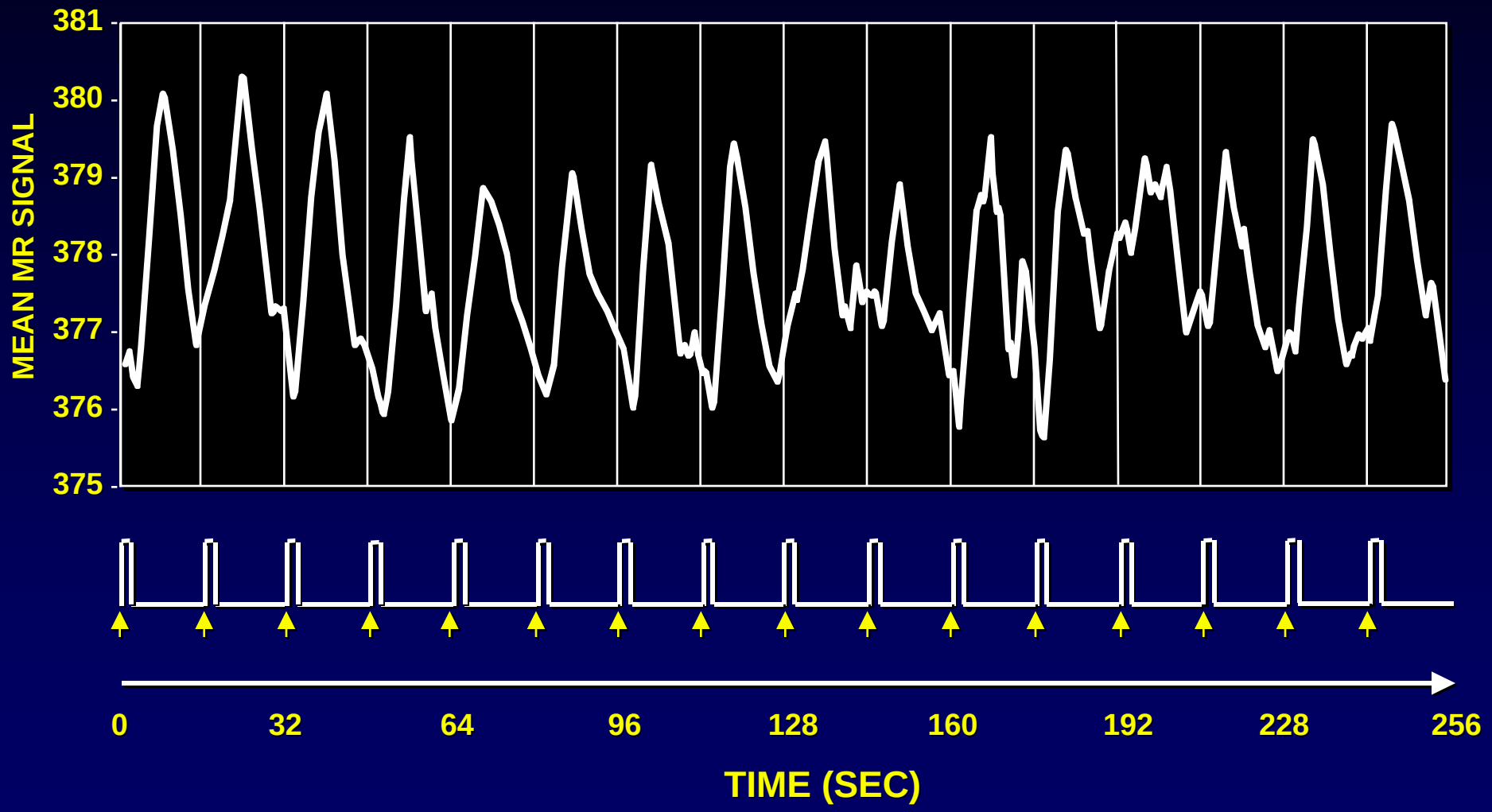


“Spaced Event-Related” fMRI: Language Paradigm

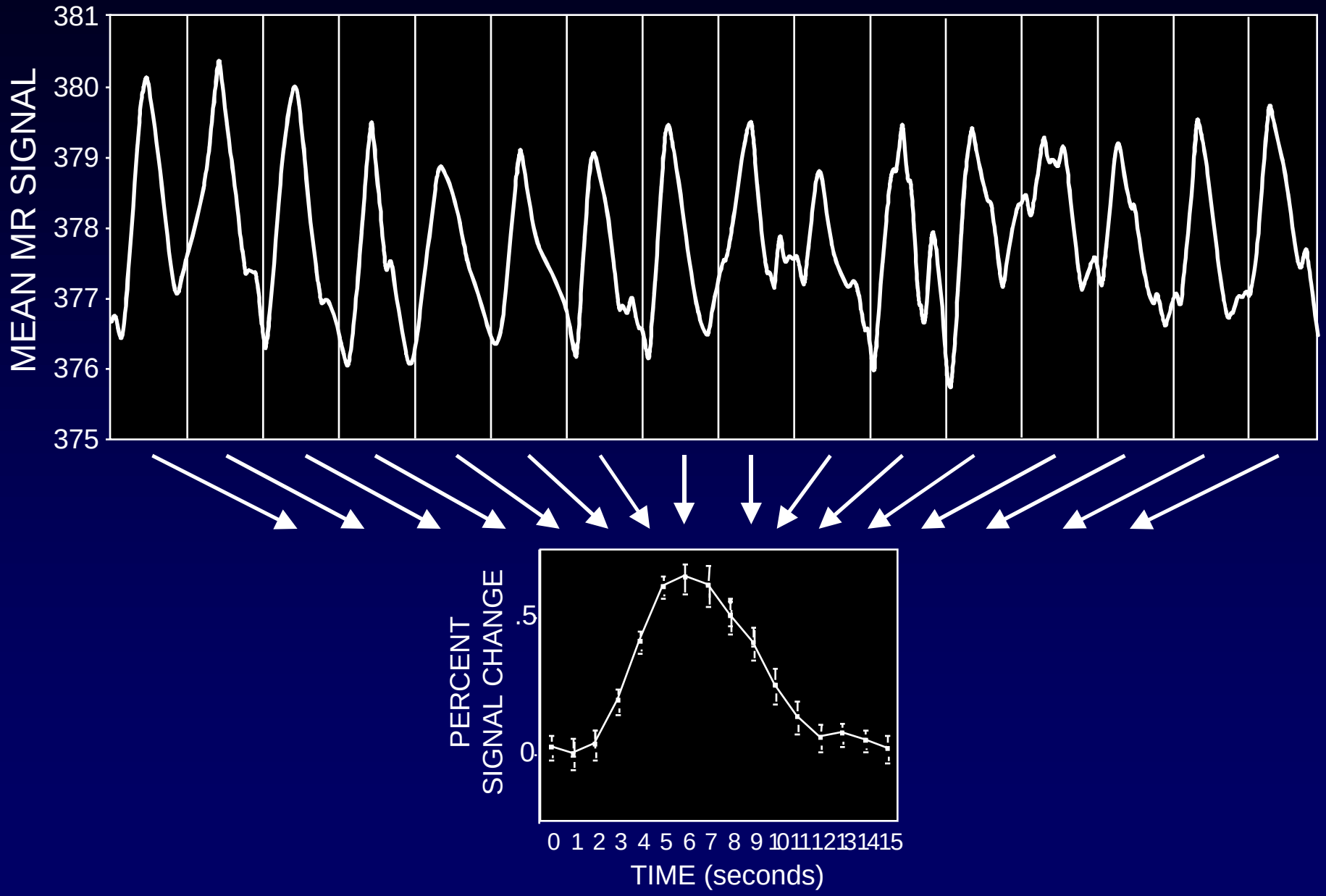


[Buckner, Bandettini et al., ***PNAS***, 1996]

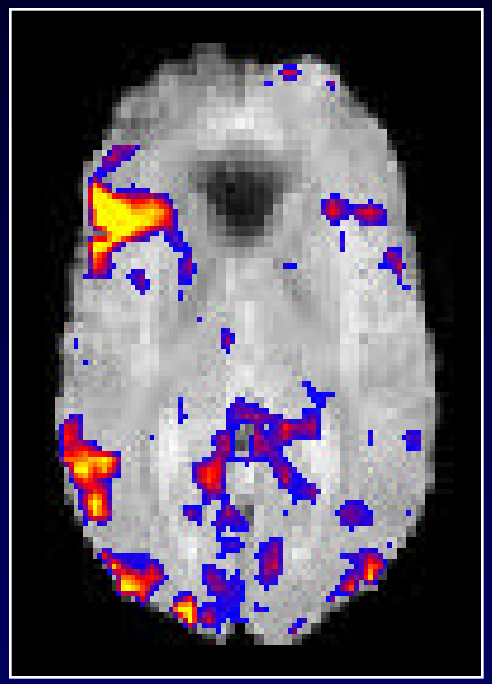
“Single-Trial” Response Across a Run

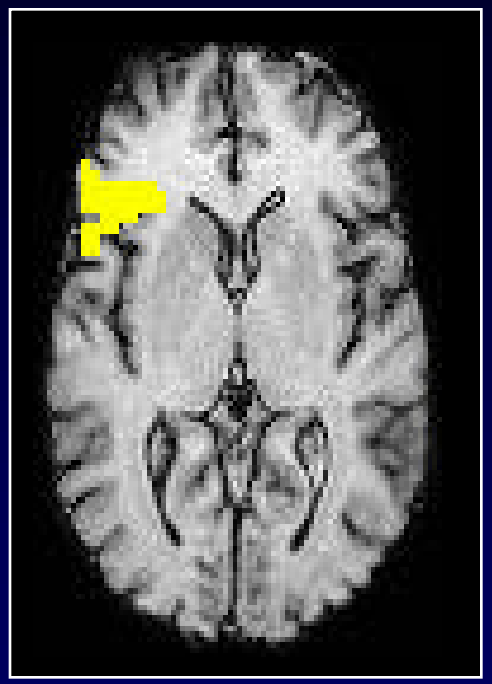


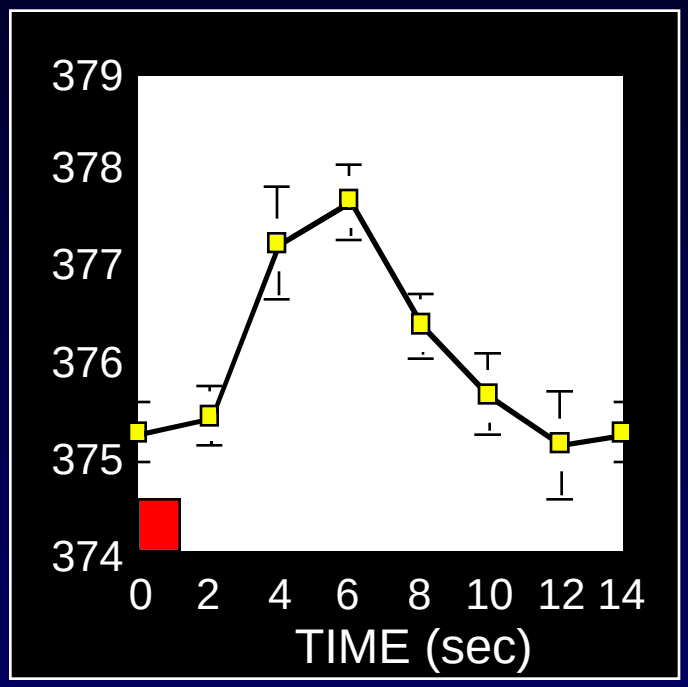
“Event-Related” Selectively Averaged Response



Broca's Area During Language Paradigm







Thanks to Randy Buckner

“Rapid Event-Related” fMRI

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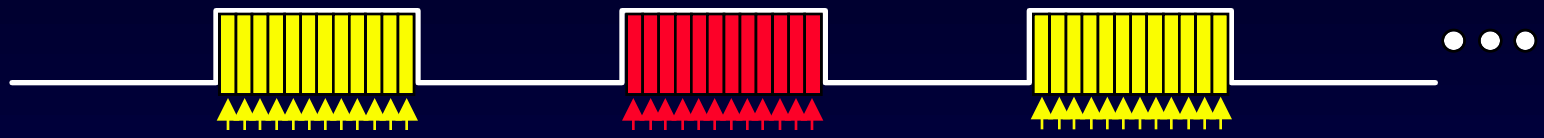
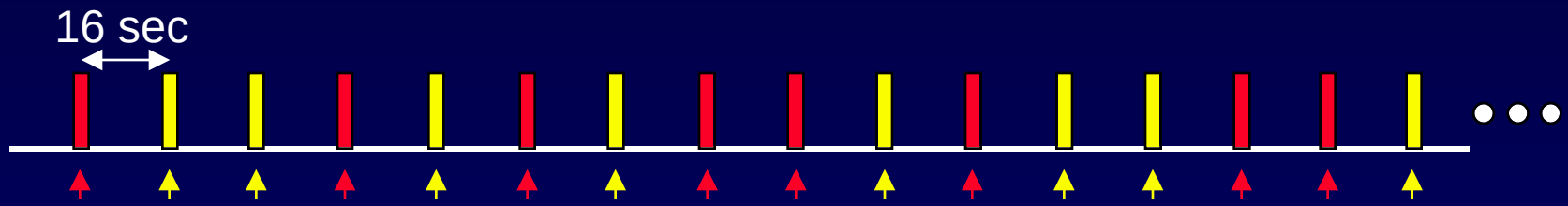
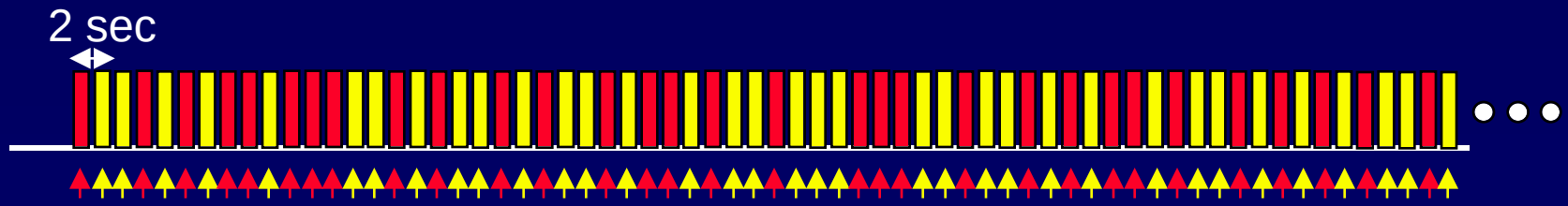


SPACED EVENT-RELATED:



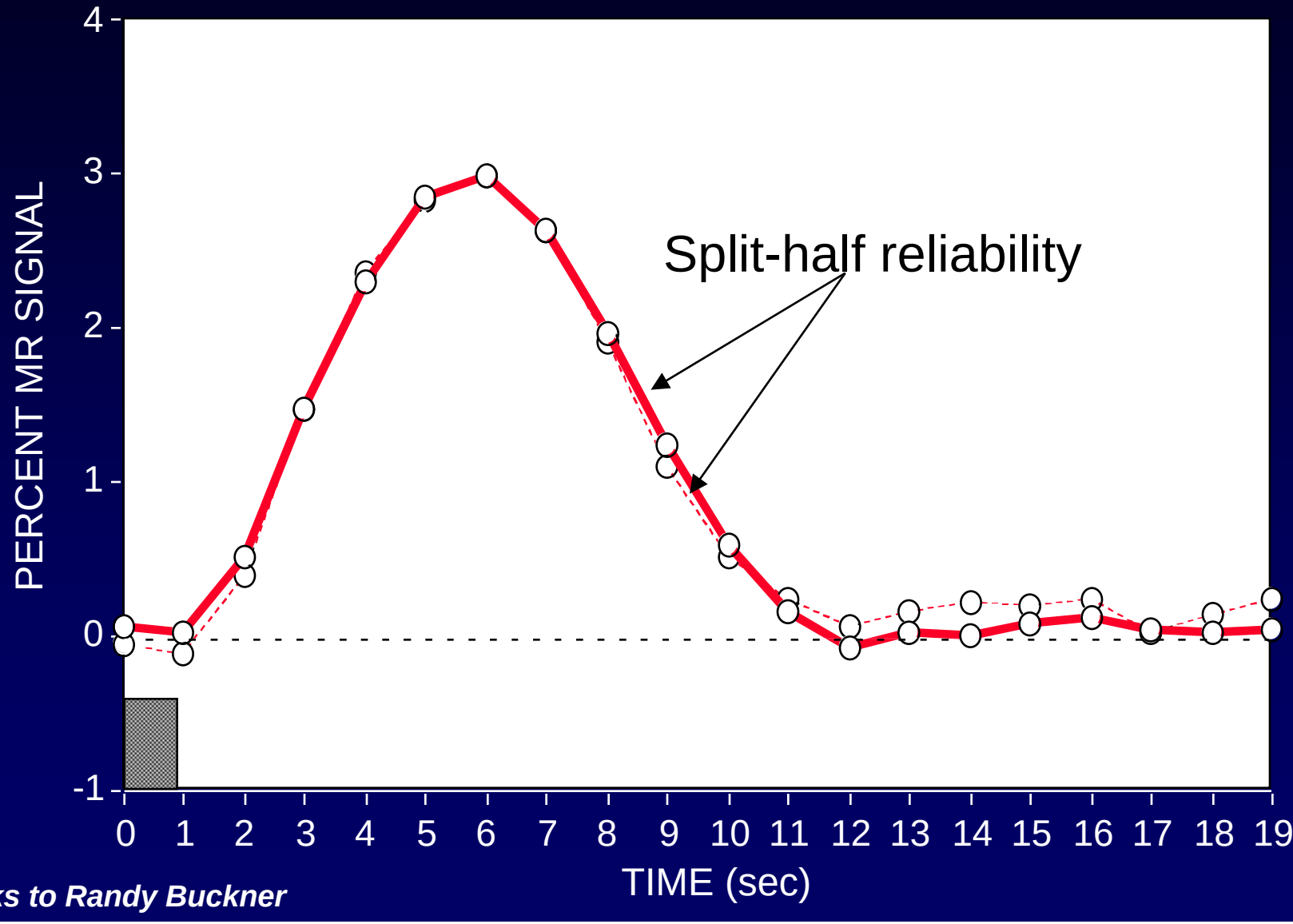
RAPID EVENT-RELATED:



Assessing the Linearity Hypothesis

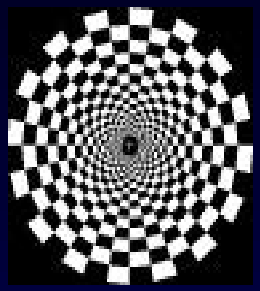
[Dale and Buckner, ***Hum. Brain Map.***, 1997]

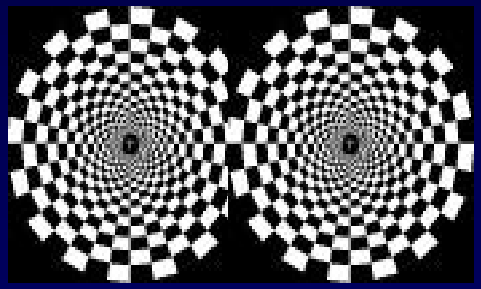
Response to Averaged Single Trials



Thanks to Randy Buckner

Assessing the Linearity Hypothesis: 5 Second ITI

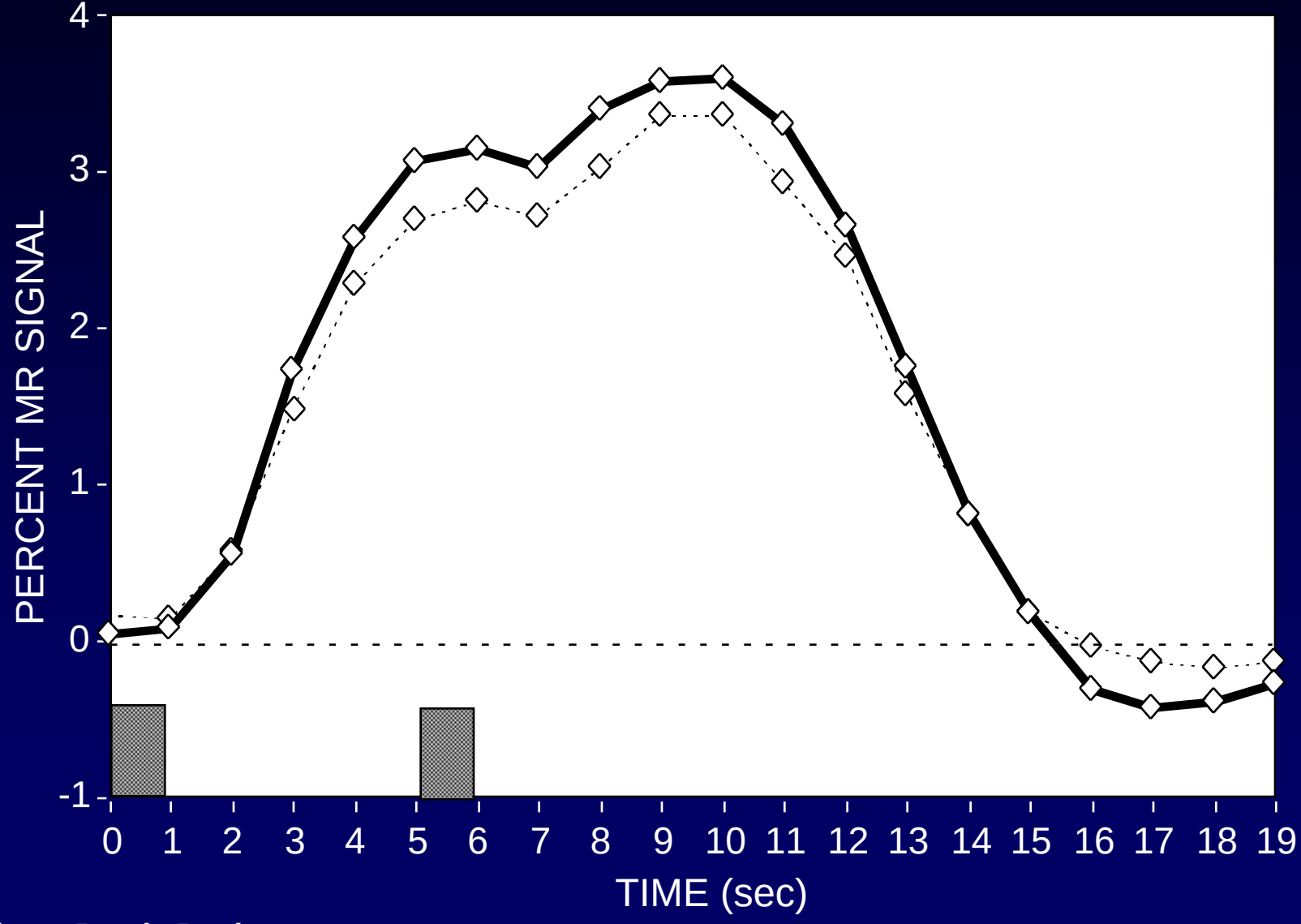




0 sec 5 sec 20 sec

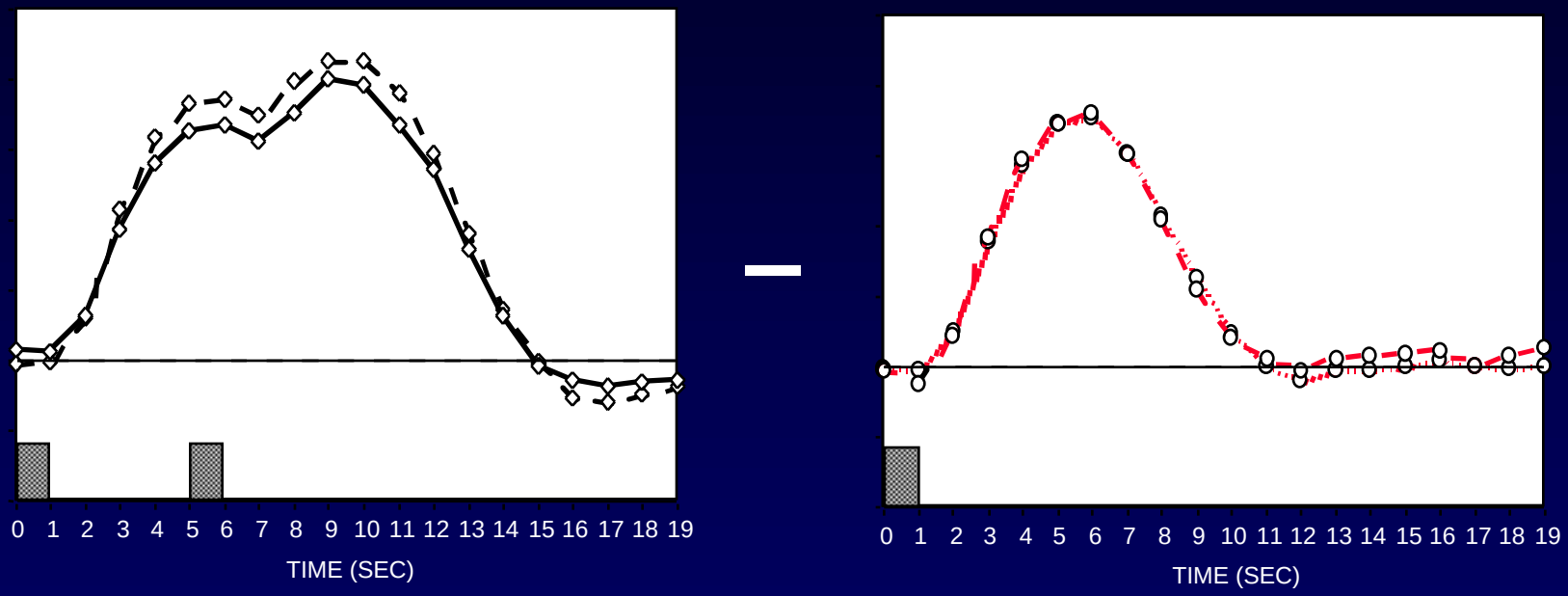
Thanks to Randy Buckner

Response to Averaged Double Trials



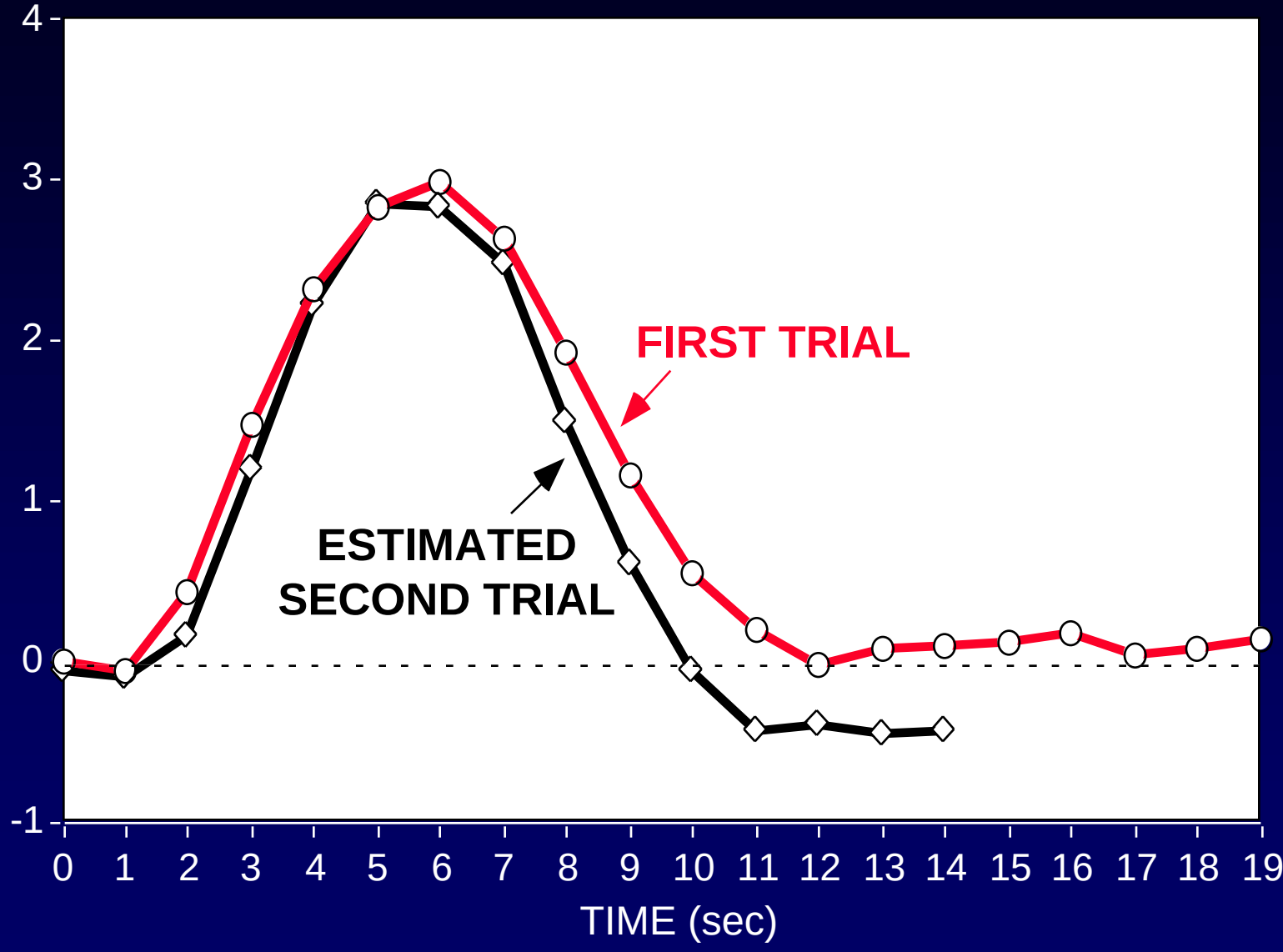
Thanks to Randy Buckner

Assessing the Linearity Hypothesis: Separation of Responses



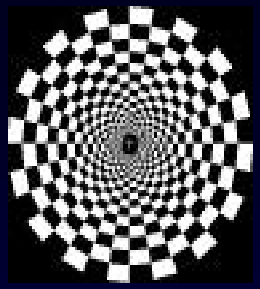
Thanks to Randy Buckner

Assessing the Linearity Hypothesis: Separation of Responses



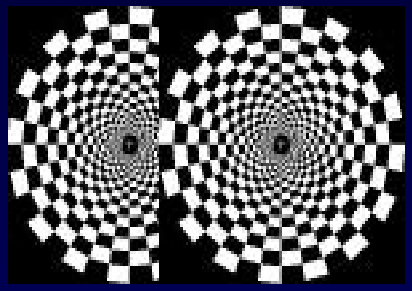
Thanks to Randy Buckner

Assessing the Linearity Hypothesis: 2 Second ITI



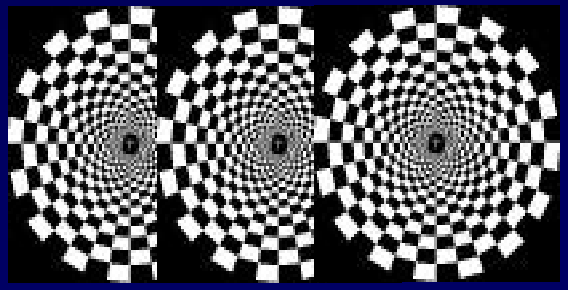
0 sec

20 sec



0 sec2 sec

20 sec



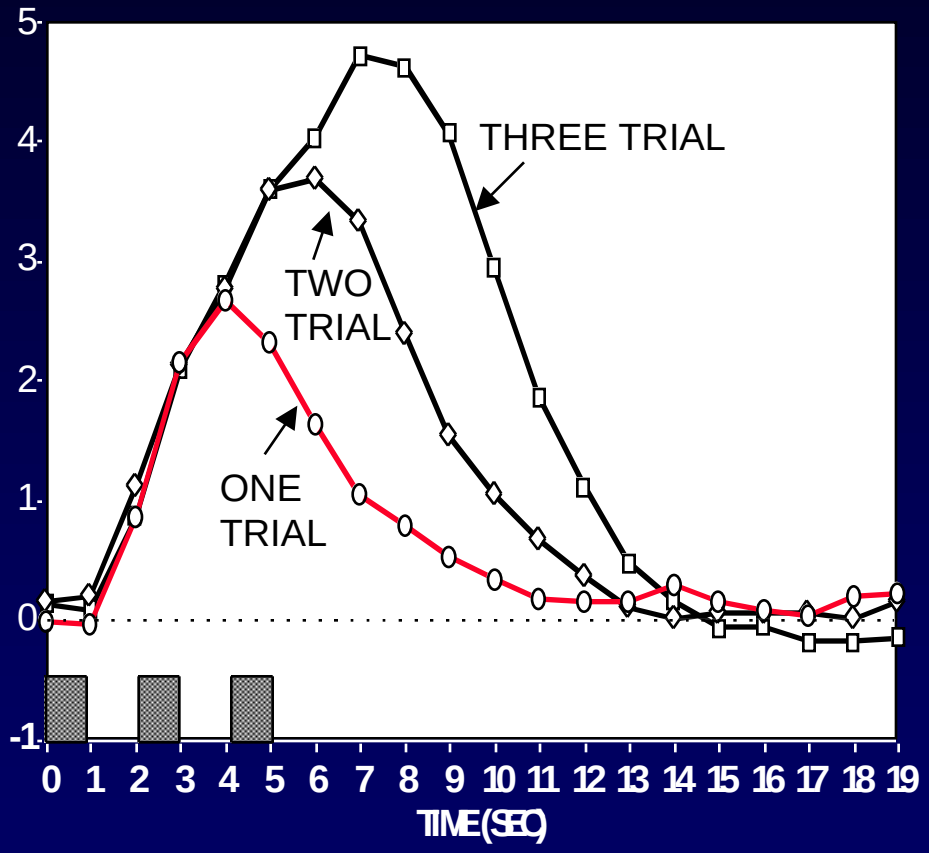
0 sec2 sec4 sec

20 sec

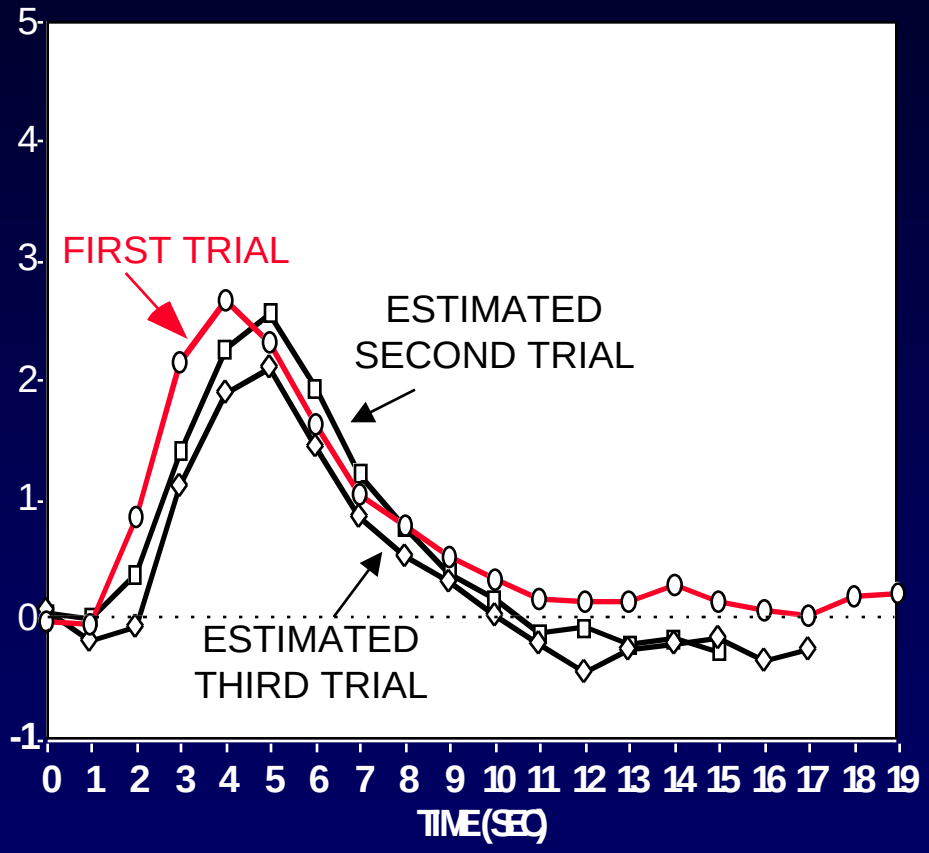
Thanks to Randy Buckner

Responses to Multiple Rapidly Intermixed Trials

RAW DATA

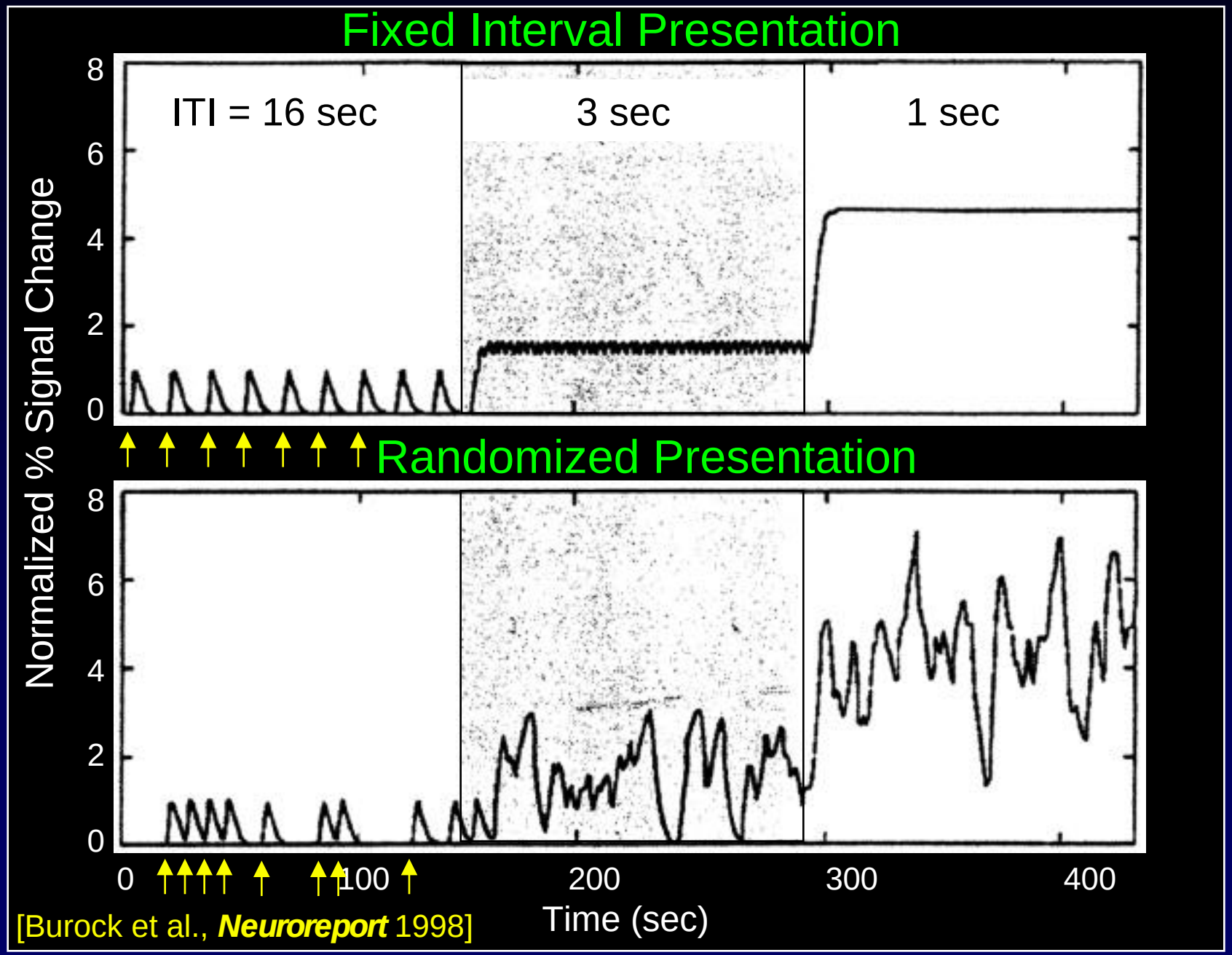


ESTIMATED RESPONSES



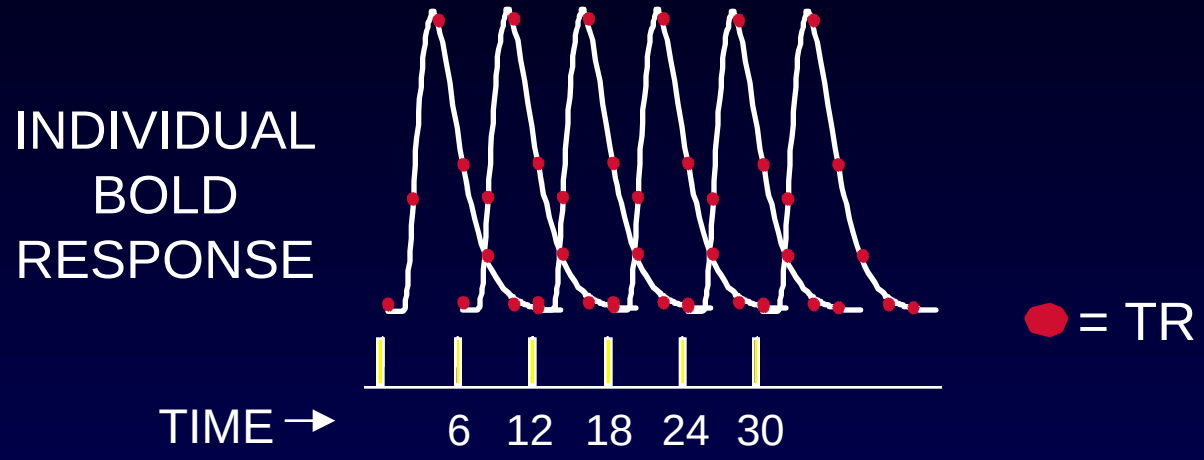
Thanks to Randy Buckner

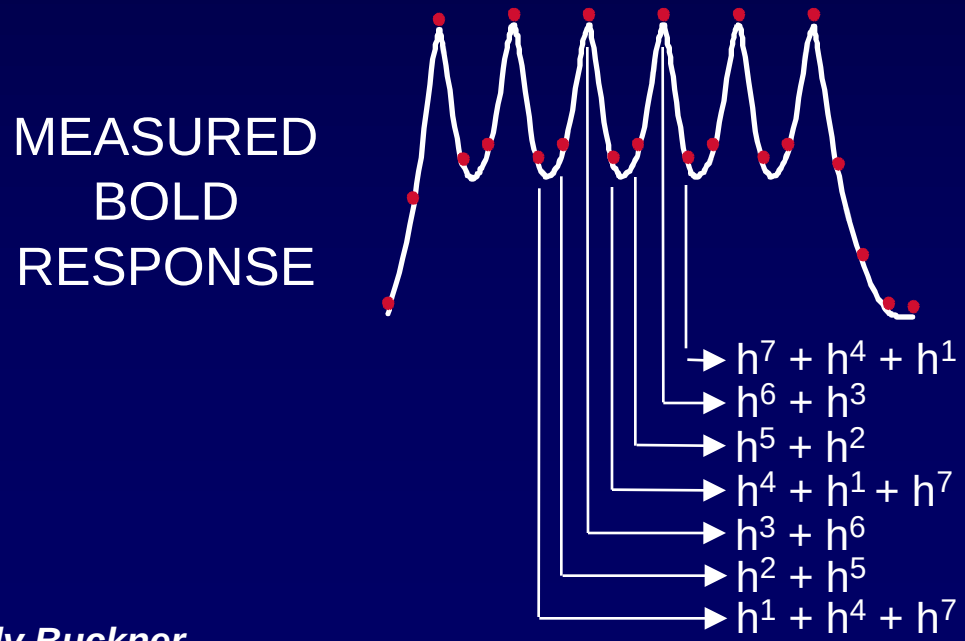
Structuring Event-Related Trial Presentations



[Burock et al., ***Neuroreport*** 1998]

Variance Associated with Fixed Interval Designs

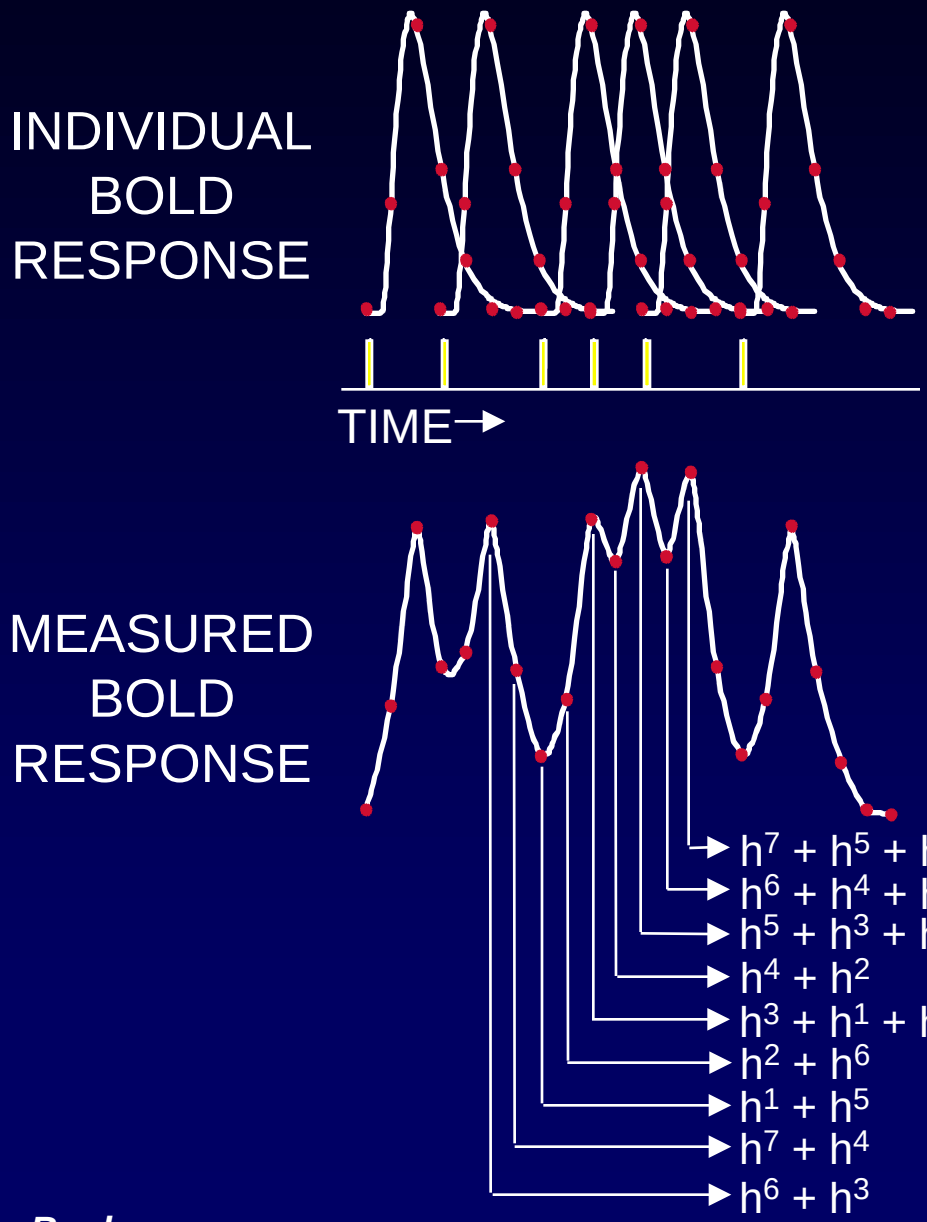




Seven unknowns, BUT only three independent equations

Thanks to Randy Buckner

Variance Associated with Jittered Designs

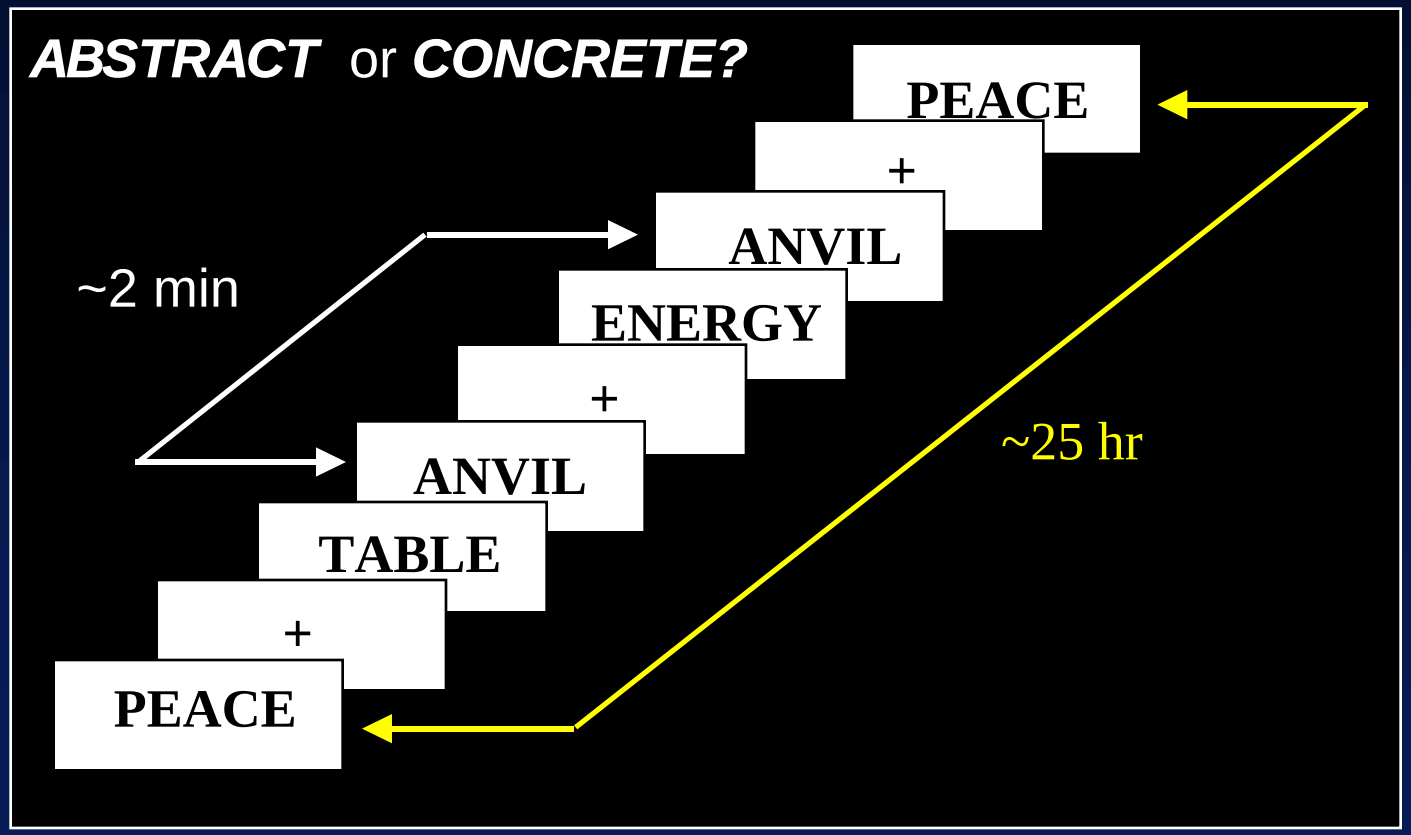


Seven unknowns, AND more than seven independent equations

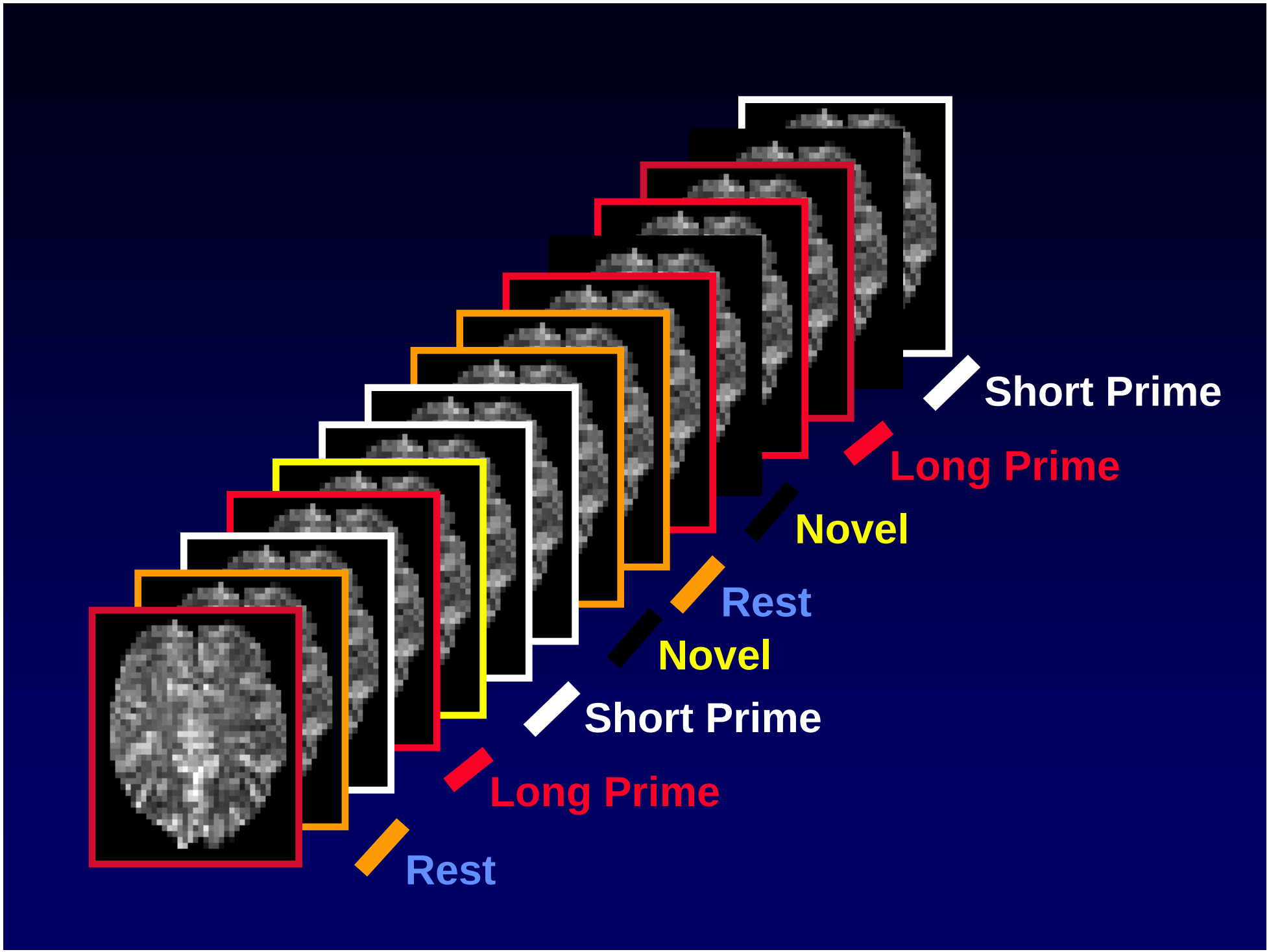
Thanks to Randy Buckner

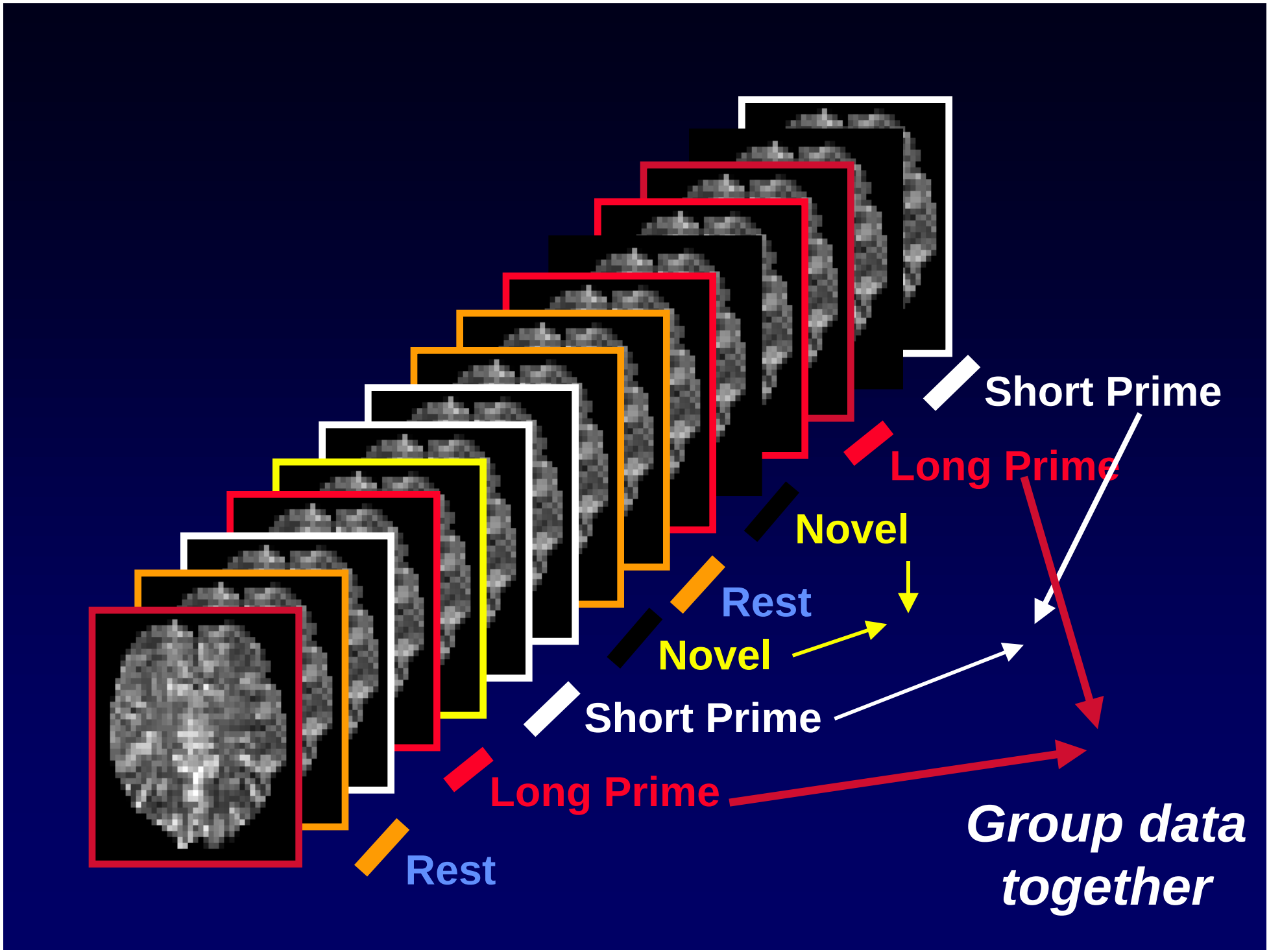
Sorting Based on Experimenter Determined Conditions

Does the neural correlate of priming vary with the lag between the first and second episode within a semantic task?



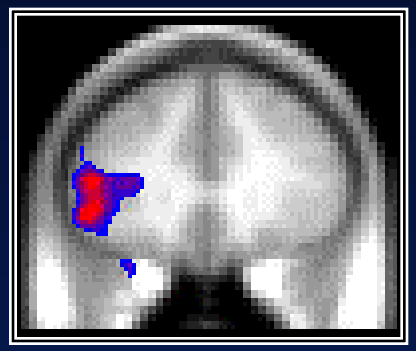
[Wagner et al., ***J. Cognitive Neuroscience*** 2000]

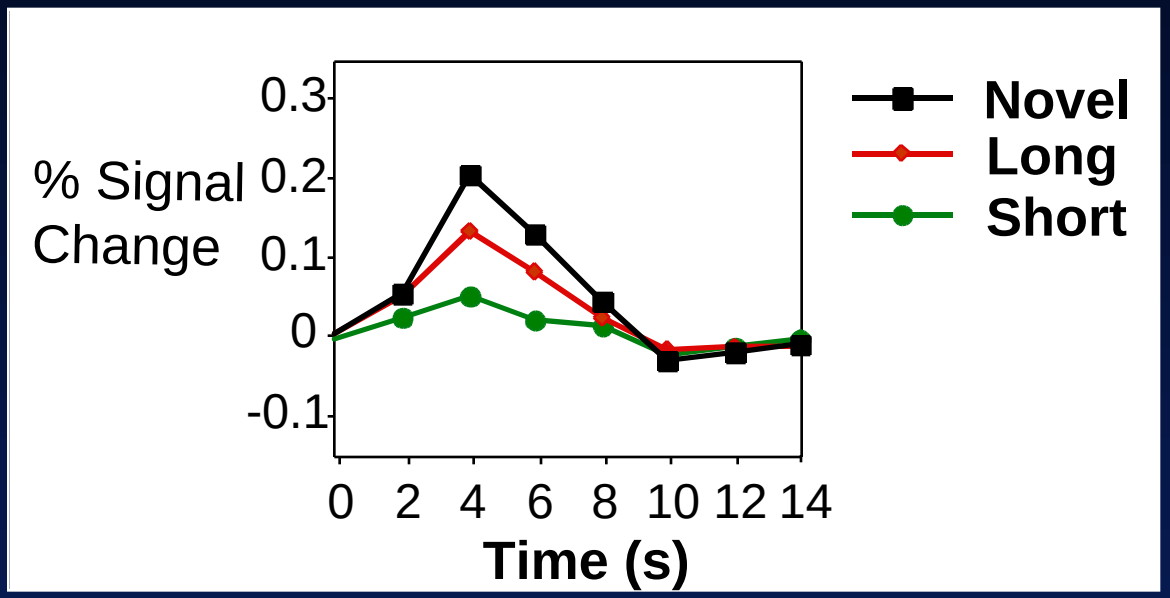

Short Prime
Long Prime
Novel
Rest
Novel
Short Prime
Long Prime
Rest


Short Prime
Long Prime
Novel
Rest
Novel
Short Prime
Long Prime
Rest
Group data together

Shorter Lags Yield Greater Neural Priming

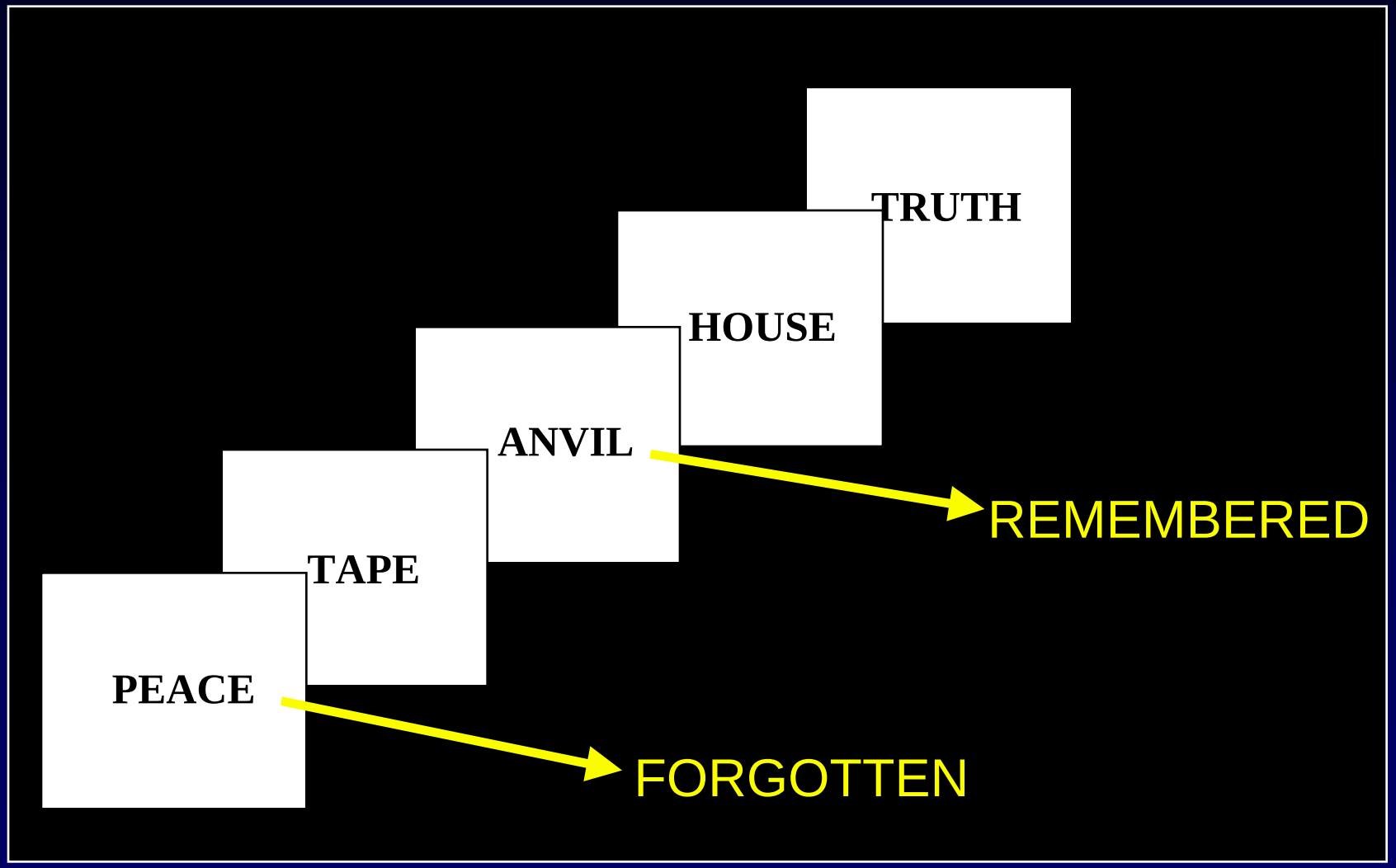
Anterior IFG





Thanks to Anthony Wagner

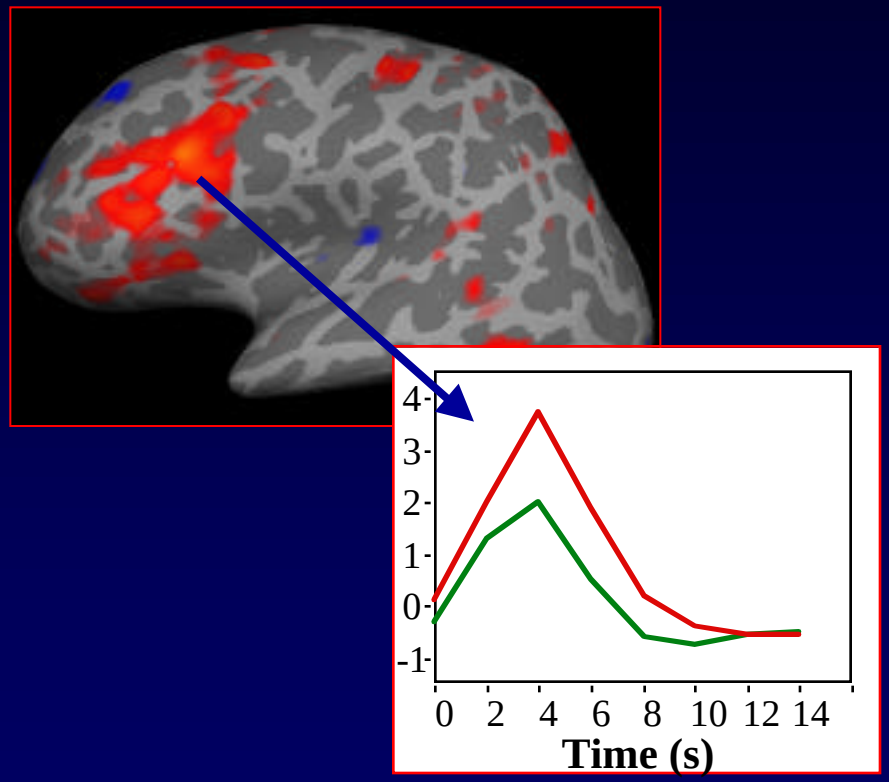
Sorting Based on Subject Behavior: Subsequent Memory Performance



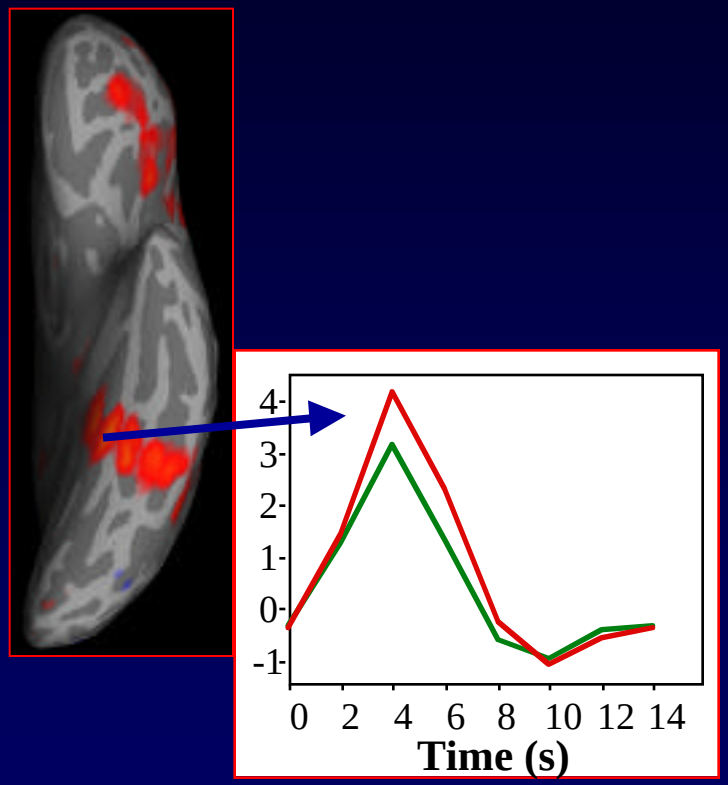
[Wagner et al., ***Science*** 1998]

Neural Regions Predicting Subsequent Memory

Inferior Prefrontal Gyrus



Left Posterior Parahippocampus



Remembered

Forgotten

Thanks to Anthony Wagner

Key Points

- What can fMRI tell you?
- Always comparing across conditions
- Characteristics of the hemodynamic response (HRF) and how this affected the sequential development of fMRI paradigms and influences study design
- Sense of important design issues

Critical issues in paradigm design

- Poorly defined neuroanatomical hypothesis
- Poorly controlled baseline
- Attentional effects
- Learning effects
- Stimulus habituation or sensitization
- System and physiological drift

Baseline, what is it?

Ex: if want to say something about verb generation and compare it only to reading aloud..

BUT, still do not know if these regions are involved in reading only (thus can include a low level reading condition..)

No inherent “0” baseline for cognition,
i.e. what are subjects doing when asked to do nothing?

- Ans: they are doing a lot
- how interpret deactivations?

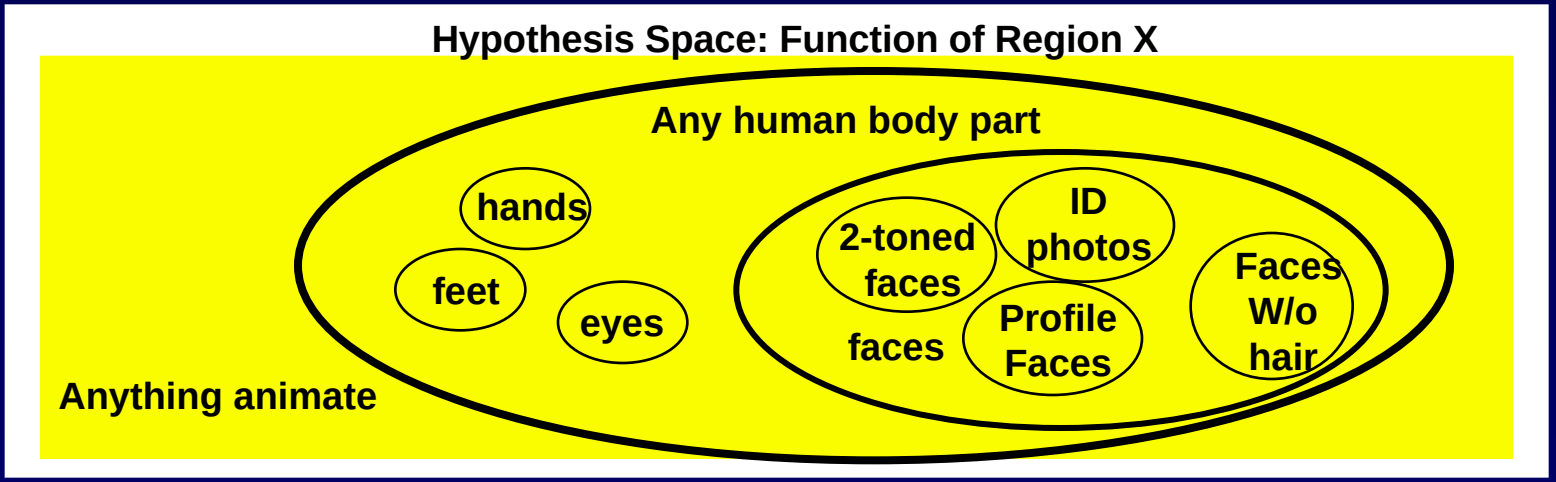
Issues: Generality vs Specificity

Hypothesis: Region X is involved in process Y.

Evidence: Region X is activated when subjects do an instance of process Y

Problem: Without running several further conditions, we can't tell whether region X might instead be involved in something either more SPECIFIC or more GENERAL than Y.

Example:



Thanks to Nancy Kanwisher

Issues: Attentional Confounds

A given region might respond more strongly in condition A than condition B simply because A is more interesting/attention-capturing than B.

Solutions:

1. Double Dissociations, i.e. faces versus objects?

2. Test conditions with opposite attentional predictions
i.e. passive viewing vs 1-back task

Thanks to Nancy Kanwisher

Issues: Statistical Significance vs. Theoretical Significance

P levels alone are not sufficient
For example, the FFA may respond significantly more to pineapples than watermelons, but the response to pineapples might nonetheless be much lower than the response to faces.

Solutions:
Quantity effect size, e.g. with percent signal change

Provide “benchmark” conditions within the same scan to give these magnitudes meaning

Objects	Watermelon	Pineapple	Faces
0.6	0.7	0.9	2.0
0.6	0.7	1.8	2.0

Thanks to Nancy Kanwisher

Acknowledgements

Anthony Wagner

Nancy Kanwisher

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Robert Savoy

Randy Gollub

Chantal Stern

Data Analysis

A. General Issues

- **Individual vs Group Analyses: brains are very different BUT want To make a general claim ANS: do both if can**

- **Multiple Comparisons….if doing 20,000 T-tests, better not accept p< .05**

B. Methods

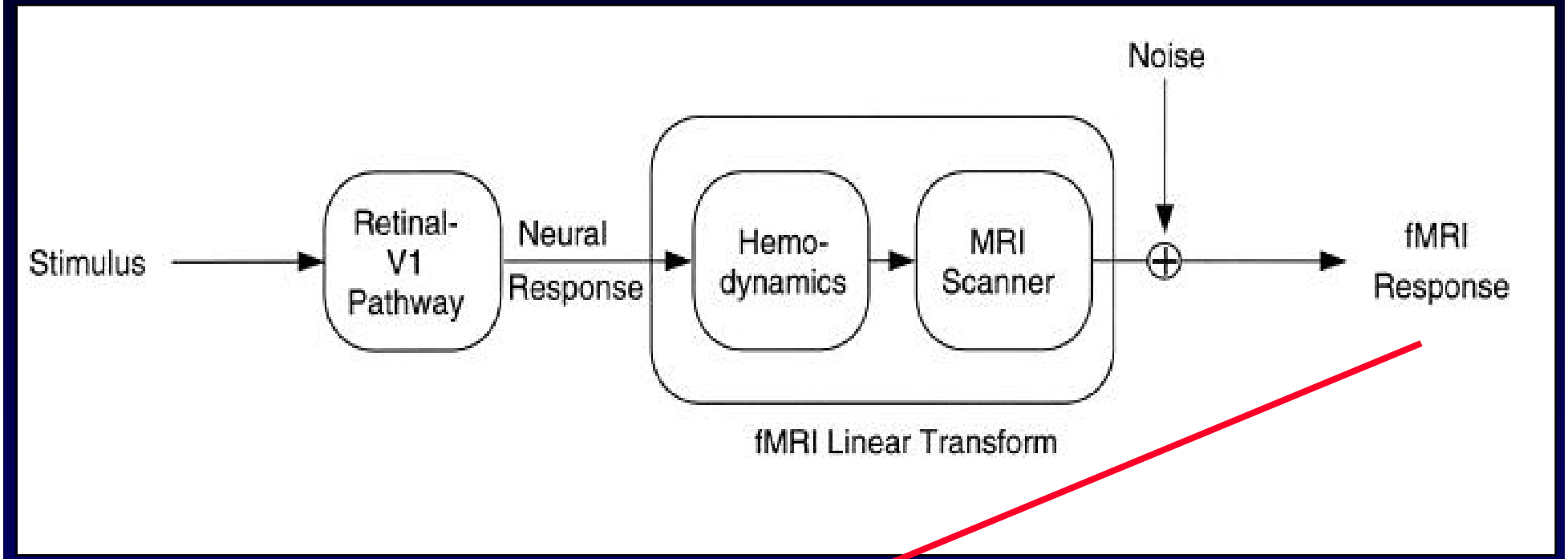
- **Simple comparisons, is X > Y ?, look in each voxel..**

- **Conjunction Analyses, are any voxels significant for both X>Y and A>B?**

- **Regression Analyses, obtaining weights for different regressors**

- **ROI-based Analyses**

Hemodynamic Response Summation: Linear Systems Approach

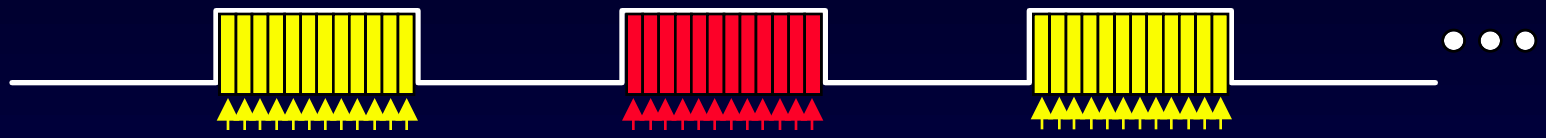


The fMRI response to a stimulus lasting a duration of NT is roughly a linear summation of N temporally shifted responses to a stimulus lasting a duration of T

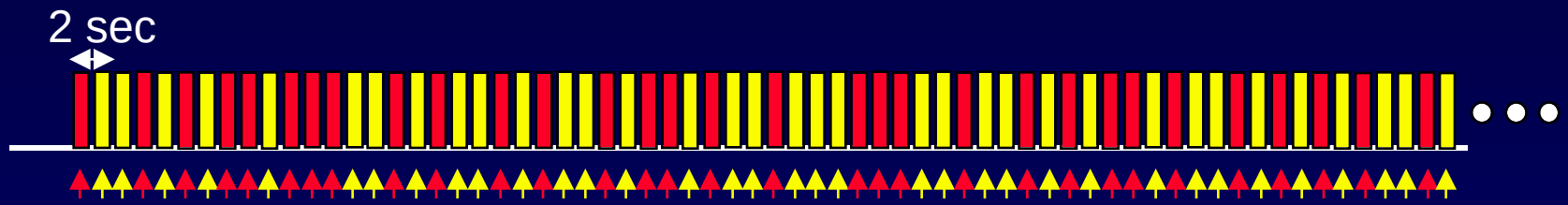
[Boyton et al., ***J. Neuroscience*** 1996]

“Mixed” fMRI

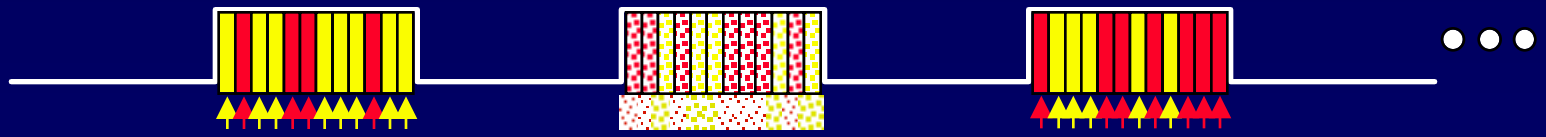
BLOCKED:



RAPID EVENT-RELATED:

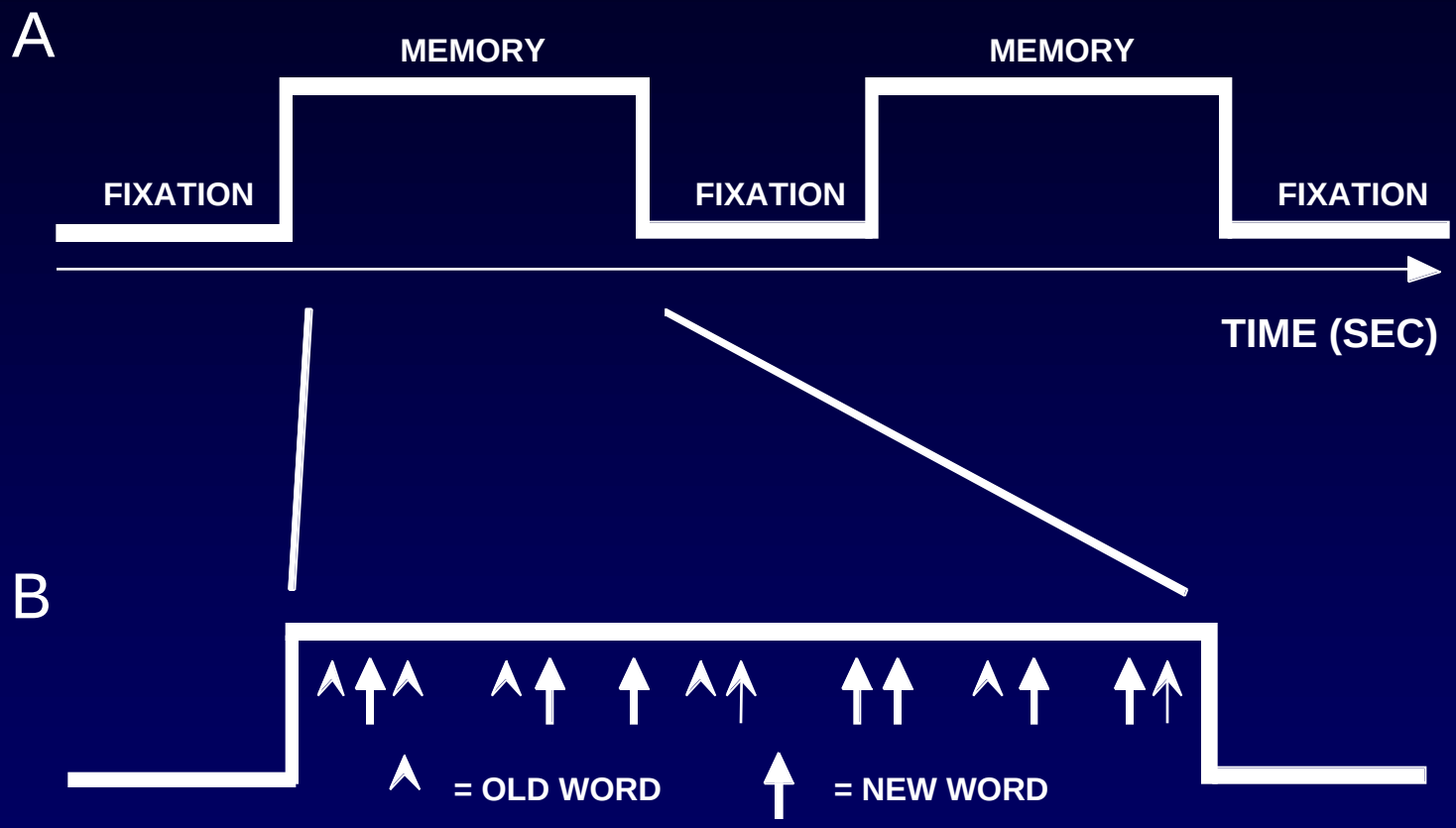


MIXED:



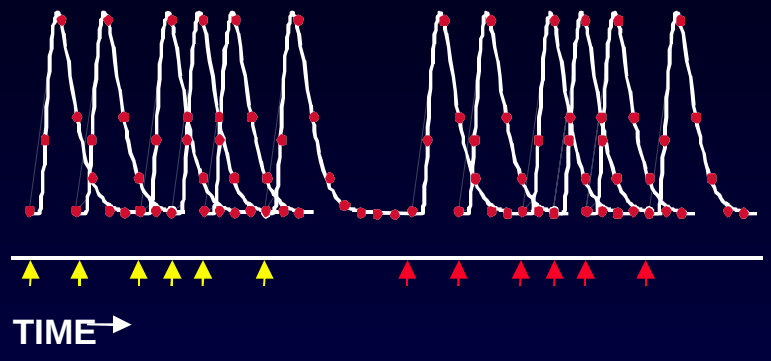
[Chawla et al., ***Nat. Neuroscience*** 1999; Donaldson et al., ***NeuroImage***, 2001]

Mixed Blocked/Event-related Design

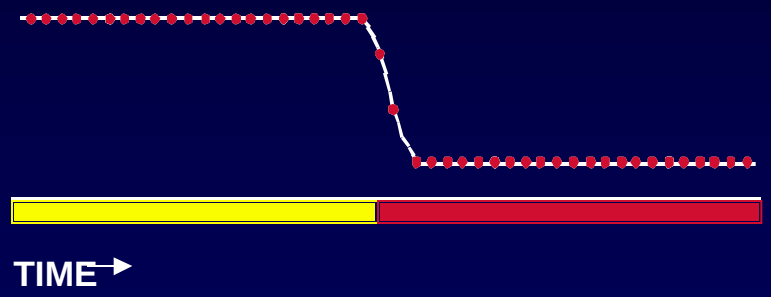


Donaldson et al., *NeuroImage*, 2001 (see also Chawla et al., *Nature Neurosci*., 1999)

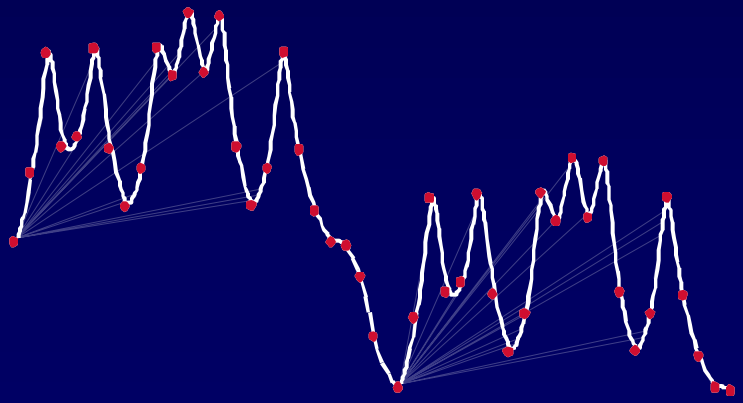
TRANSIENT BOLD RESPONSE TO EVENTS



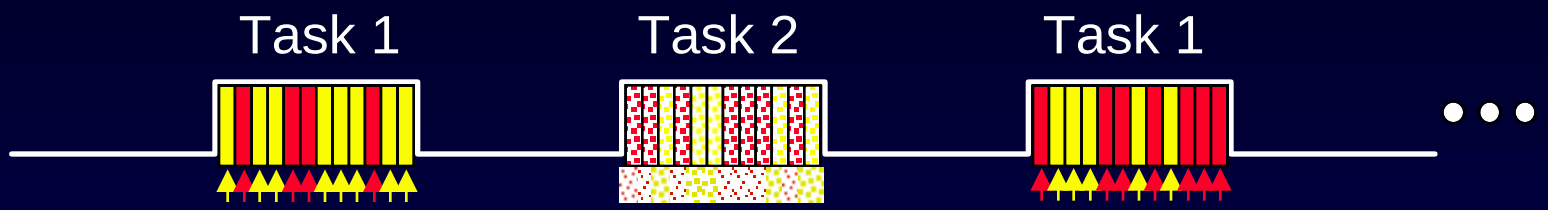
SUSTAINED BOLD RESPONSE TO SET



MEASURED BOLD RESPONSE



“Mixed” fMRI:
Trial Separation with Task Blocking

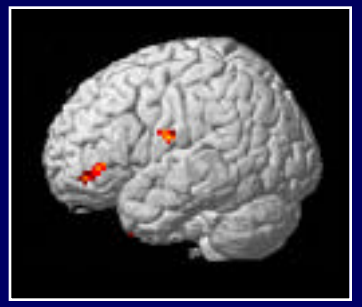


Analysis Strategies:

– Event-related analyses

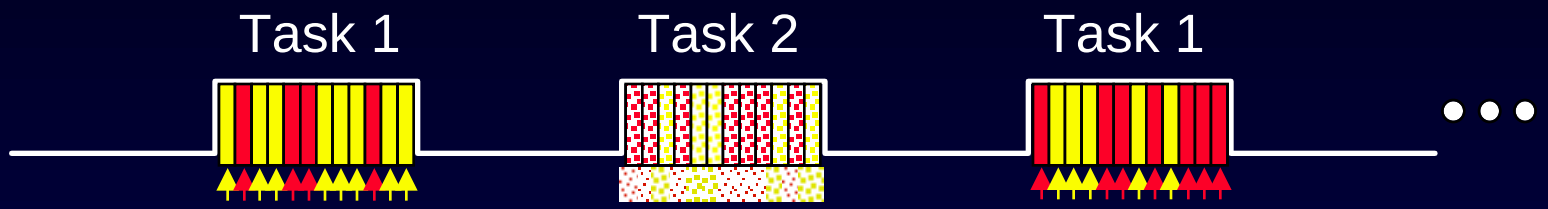
- Task 1 trials ( ) vs. Task 2 trials ( ) →

- Trial type A ( ) vs. Trial type B ( ) →



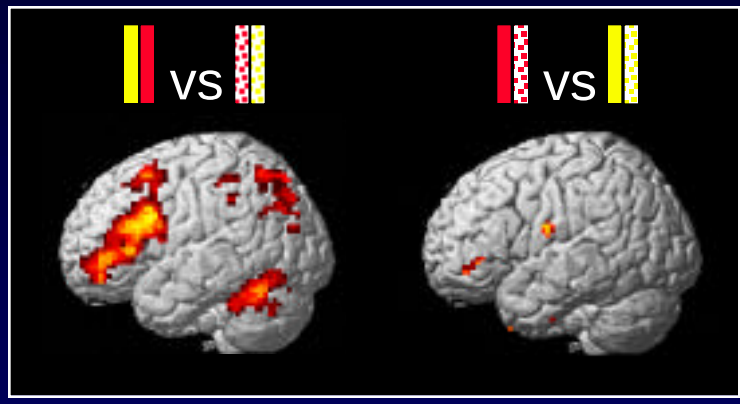
[Badre et al., ***in prep.***]

"Mixed" fMRI:
Trial Separation with Task Blocking

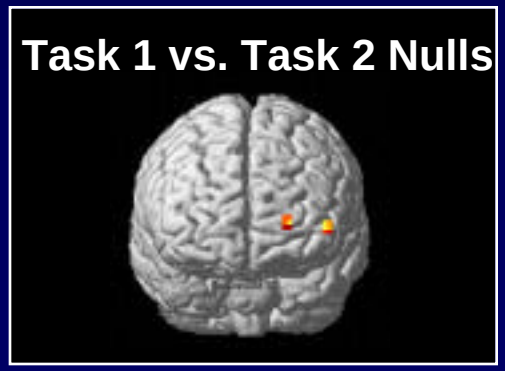


Analysis Strategies:

– Event and State effects
  - Same event contrasts



  - Also model NULL components within blocks to explore "state" effects



CAVEAT: correlation between event and state regressors