Experimental Design for Imaging I

Susan Bookheimer
UCLA School of Medicine

Conceptual and methodological aspects of experimental design

- There are two aspects of fMRI design that are important to distinguish
- Conceptual design
  - How do we design tasks to properly measure the processes of interest?
  - The issues here are very similar to those in cognitive psychology
- Methodological design
  - How can we construct a task paradigm to optimize our ability to measure the effects of interest, within the specific constraints of the fMRI scanning environment?

IV's and contrasts: basics

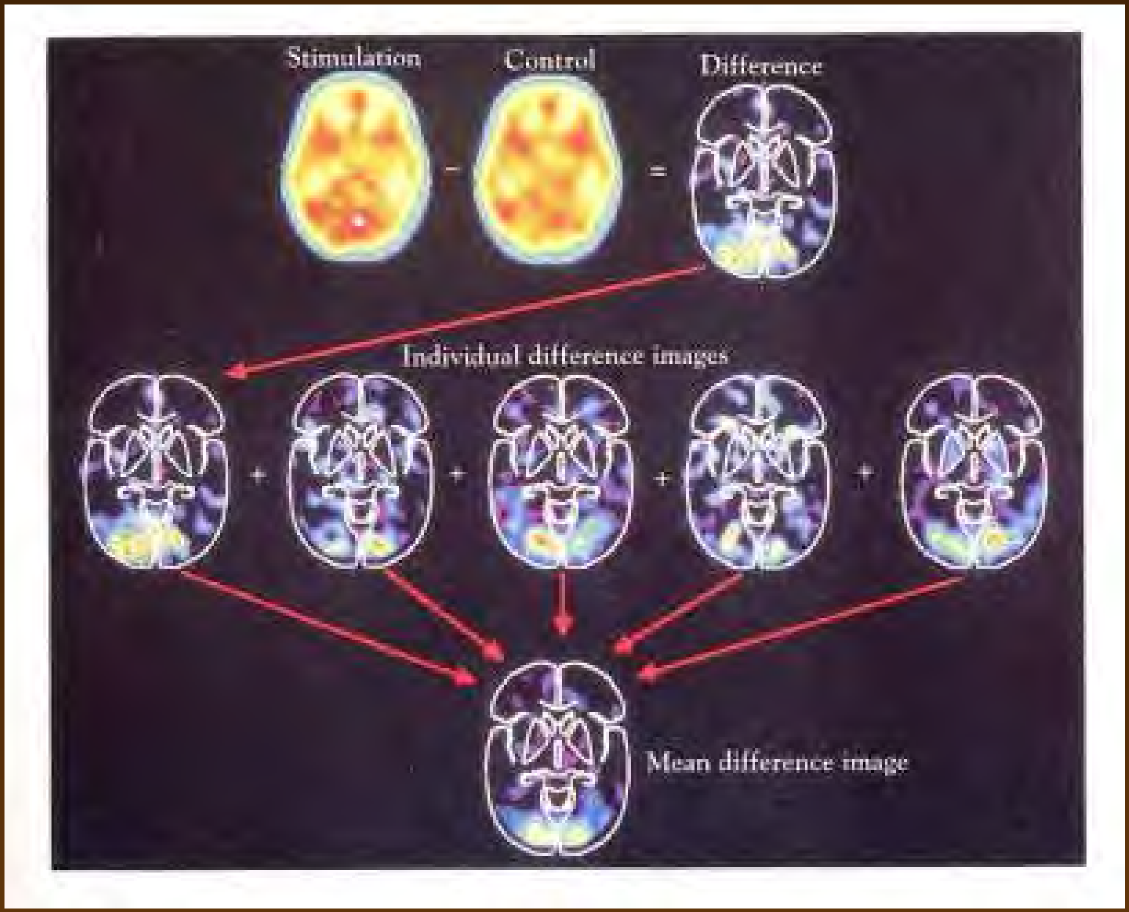
- There are (almost always) two or more conditions in activation imaging
- We make a series of assumptions about the **cognitive** and the **neural** processes involved, and their relation to each other, in every experiment
- The logic involved and choosing tasks and contrasting them, and the problems of assumptions in these choices, spans all experimental designs
- In this context, makes no difference whether we use event related or blocked designs, eg. "Null" events in ER designs often = "rest" in block designs

Design Structures

- Subtraction designs
  - Simple; hierarchical; Parallel; tailored
- Factorial
- Parametric
- Selective attention
- Conjunction
- Priming/adaptation
- Functional Characterization
- Mixed/nested
- 2-Group

The subtraction method

- Acquire data under two conditions
  - These conditions putatively differ only in the cognitive process of interest
- Compare brain images acquired during those conditions
- Regions of difference reflect activation due to the “subtracted” process of interest



Petersen et al., 1988

Simple subtraction

Exp Task - Control Task =
Process of Interest

- Task Analysis Assumptions: Make assumptions about
  - What your tasks are doing- do they tap into the processes of interest
  - How they differ (what variables are shared, what are unique)
  - Rarely tested experimentally
- Pure Insertion Assumption
- Often assume that differences are due to increases in one condition- that which is the "higher order" task or the experiment (vs. control) task. "Experimental Increase" assumption

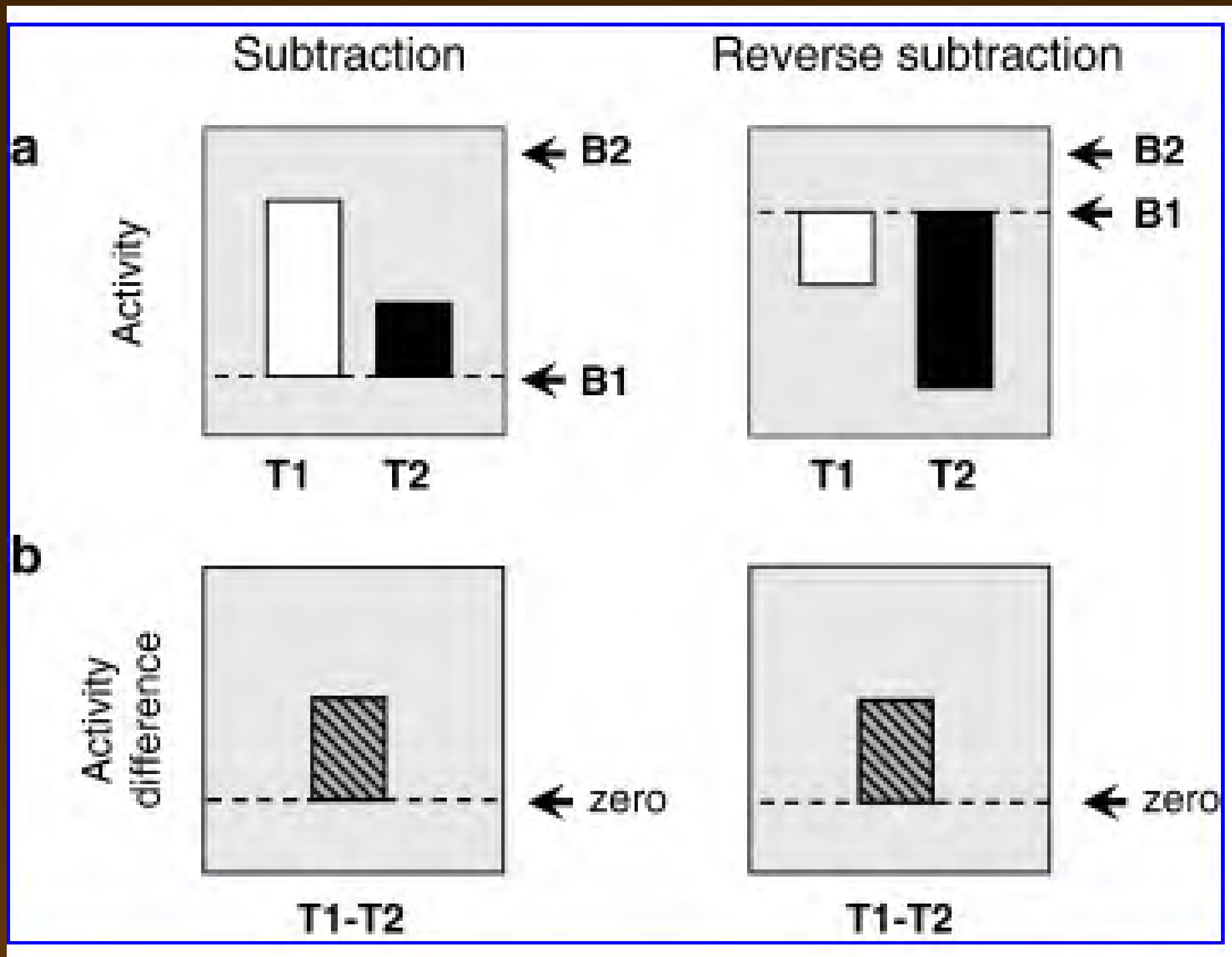
The task analysis assumption

- Subtraction assumes that the task analysis is correct
  - In particular, no other processes are implicitly engaged by the baseline task, even if they are not required
- Example
  - Subtraction of word naming from verb generation
  - What if people automatically engage semantic processes even if the naming task doesn't require them?
- Example
  - Instructions to remember, vs passive presentation

The pure insertion assumption

- Subtraction requires a strong assumption of “pure insertion”
  - Insertion of a single cognitive process does not affect any of the other processes (no *interactions*)
- Failure of PI means that the results cannot be interpreted with regard to the specific cognitive process of interest
- Multiple hierarchical contrasts compound your assumptions
- PI must hold at both neural and cognitive levels

Experimental Increase assumption



From Morcom and Fletcher, NeuroImage, 2006

Subtraction Designs

Simple

Exp Task – Control
= Process of interest

Hierarchical

Ex B
–
Ex A
–
Control

Common baseline

Ex A → Control ← Ex B

Parallel

Ex B > Ex A

Ex A > Ex B

Tailored Baseline

Ex A > Ctl A

Ex B > Ctl B

>}

Hierarchical subtraction

example from Petersen, 1991

- Rest Control
- Passive listening to words - rest
- Repeating heard words - passive words: motor areas
- Generating words - repeating: semantic (language) areas

} Sensory

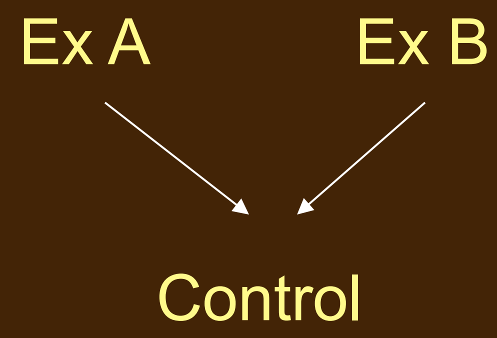
} Motor

} Semantic

Strong assumption of pure insertion, at multiple levels:

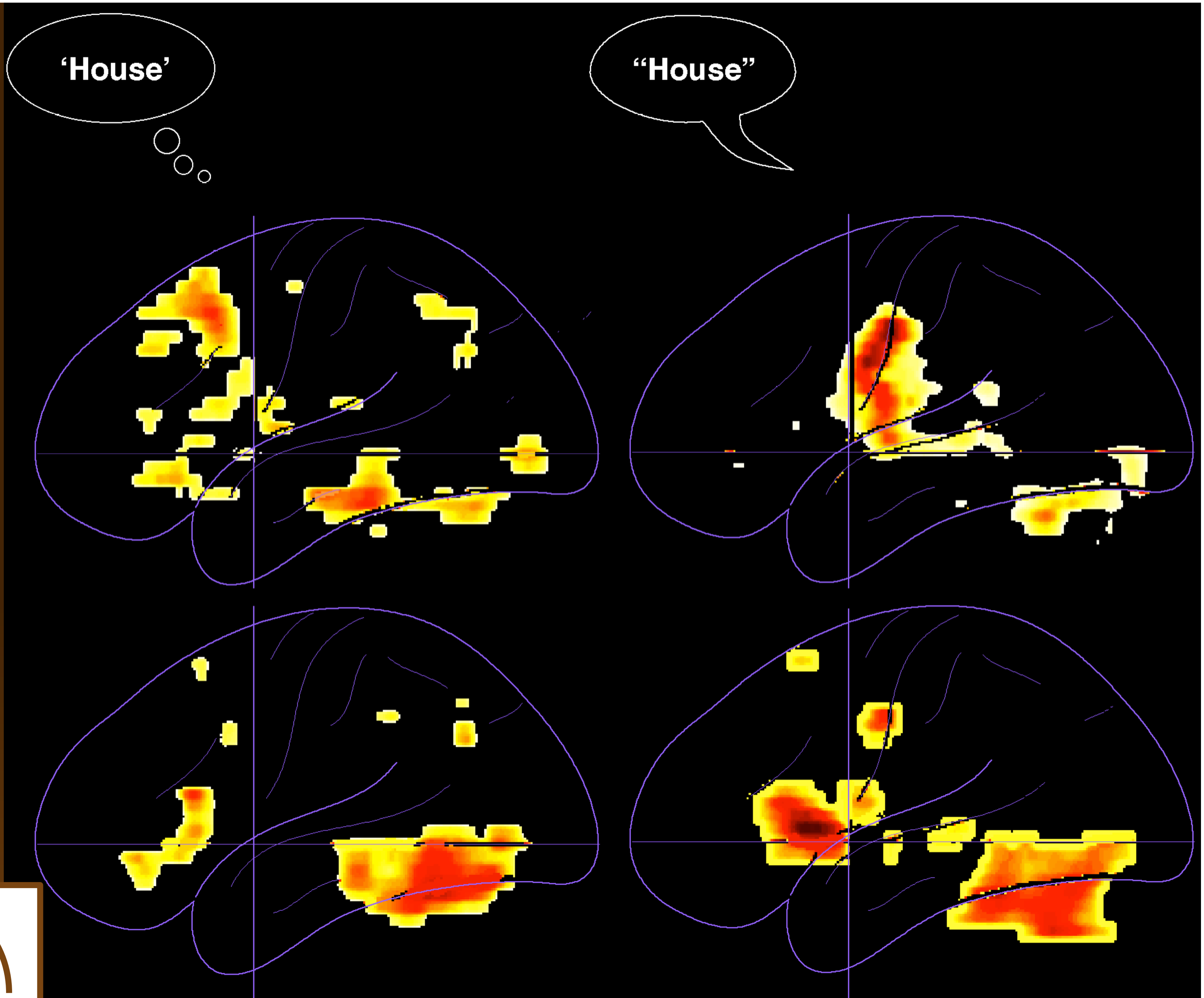
Does passively listening to words activate language areas?

Common Baseline

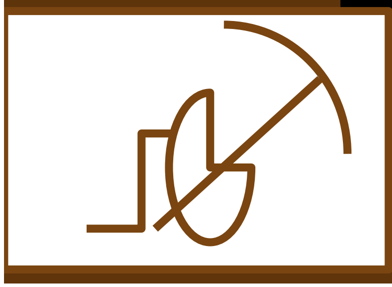


- One level of hierarchy
- Test for violation of additivity assumption
- Allows you to see common areas active for A and B
- Assumes A and B have similar psychometric properties (ie, level of difficulty, variation, and distribution in the population)
- Need additional approach to see unique areas

Read
"HOUSE"



Name



Ex B > Ex A

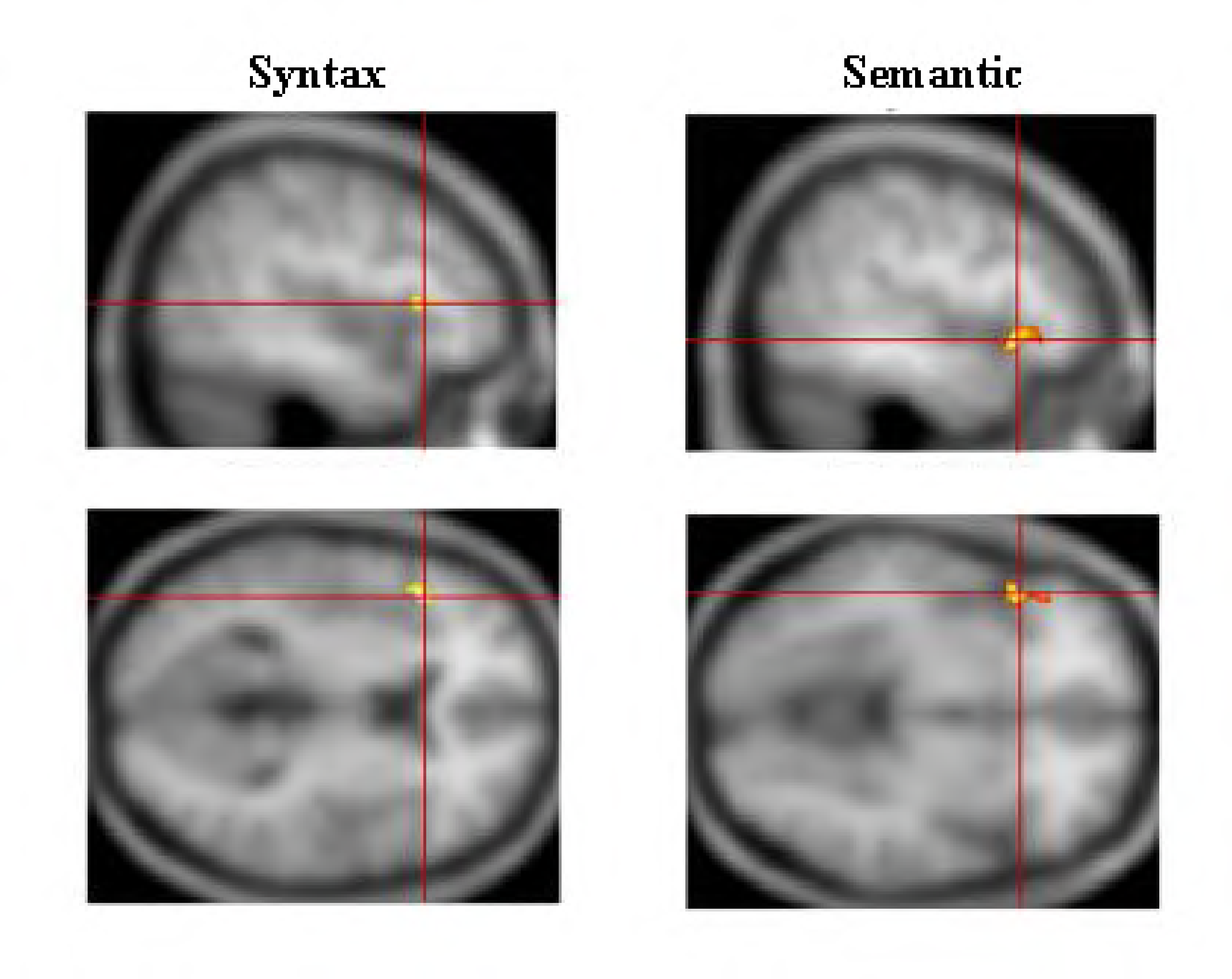
Ex A > Ex B

- **Parallel Comparisons**
  - Task A vs B; B vs A
  - EG: silent vs. oral reading and reverse
  - EG: Seeing words vs. hearing words
  - Alone, see no common areas
  - Good adjunct to common baseline
  - Use common baseline as mask to reduce errors and increase power in likely areas
  - Assumes similar psychometric properties of A and B

Are there unique divisions within IFG for syntactic vs. semantic aspects of sentence comprehension?

Syntax > Semantics;   semantics > syntax

45



47

Dapretto and Bookheimer, Neuron, 1999

Subtraction vs. Factorial Design
Object recognition vs. "Phonological retrieval"

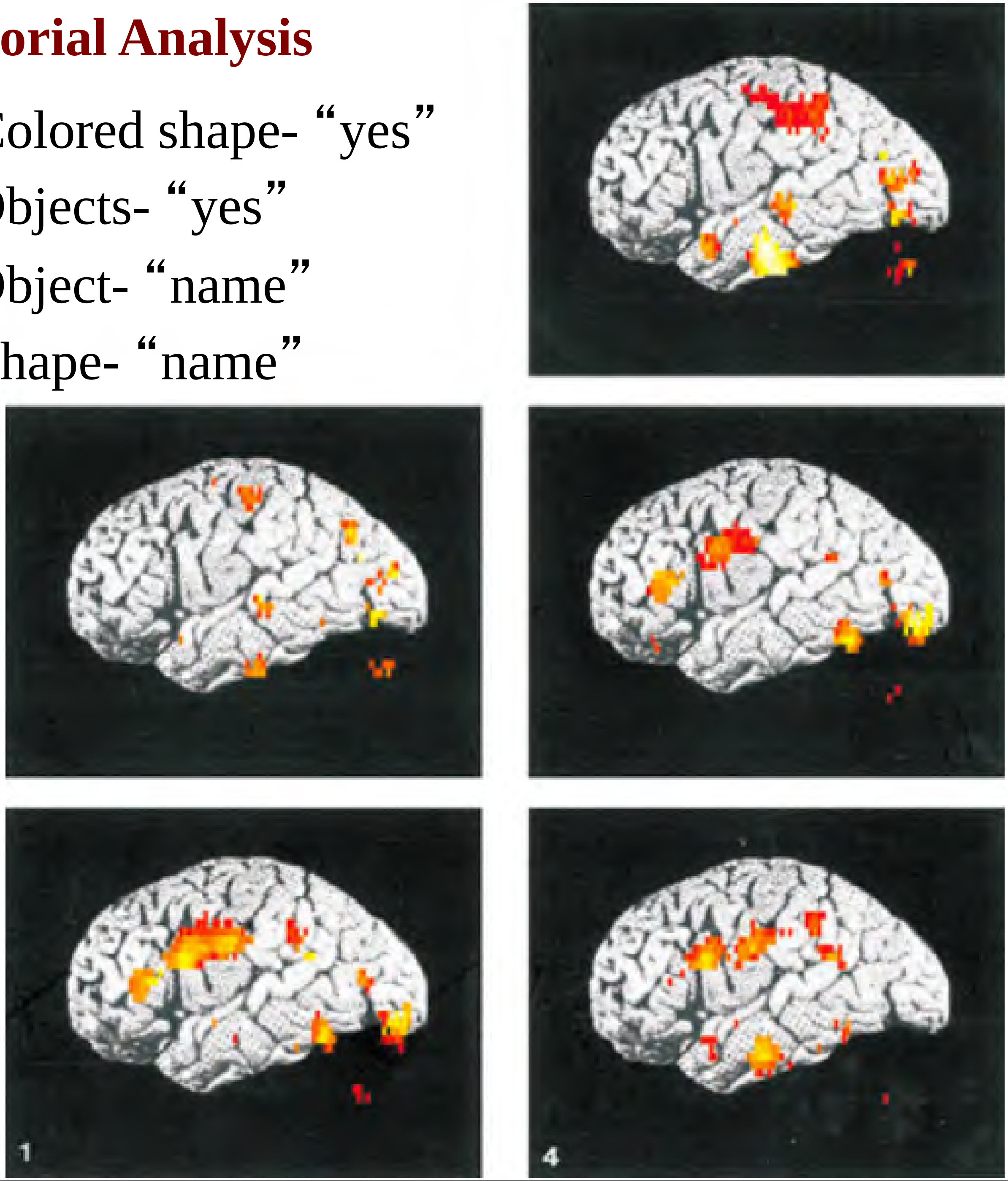
- A. Colored shape- "yes"
- B. Objects- "yes"
- C. Objects- "name"
- D. Colored shape- "name"

B-A: Activation due to object recognition
C-D: Activation due to object recognition in the context of phonological retrieval
By pure insertion, B-A should equal C-D
i.e., object recognition centers are activated the same regardless of where or not the subject is naming them

From Friston, Price et al 1996

Factorial Analysis

- A. Colored shape- "yes"
- B. Objects- "yes"
- C. Object- "name"
- D. Shape- "name"



(B+C)-(A+D)

Main effect of object rec

B-A

(D+C)-(A+B)

Main effect of phonol retr.

C-B

(C-D)-(A-B)

interaction

Tailored baseline

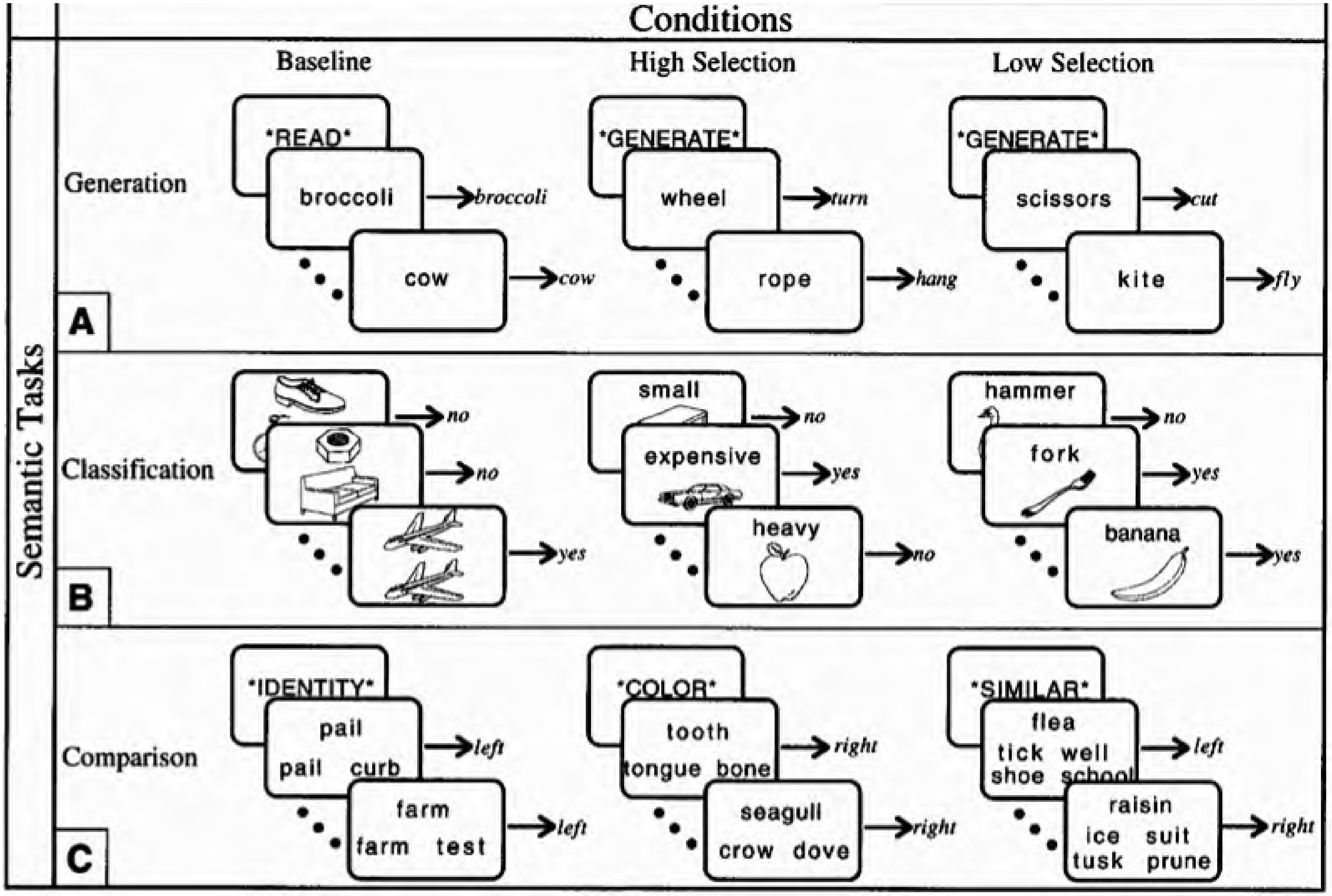
- Different control task for 2 experimental tasks
- EG: printed words vs. false fonts, heard words vs. nonsense speech
- Assumes baseline tasks control for (sensory input) equally
- Assumes similar psychometric properties of both experimental and both control tasks: rather unlikely
- Add an additional common baseline

Tailored baseline

Do visual language and auditory language stimuli share semantic representations?

- *Want to look only at semantic areas, not sensory areas- tailor control tasks for each experimental tasks, each control task matched for unwanted variables*

- Example study (Thomspon-Schill, PNAS 1997): Do frontal areas implicated in semantic processing really involve semantics, or are they instead important for response selection (independent of task)
- Use 3 different tasks: generation, classification, and comparison; each has its own control, each as different levels of selection demand



Thompson-Schill et al PNAS 1997

- In such a design you make multiple assumptions
  - Of pure insertion
  - Parametric assumptions: The relationship between task and control is the same across different tasks
  - The differences across hierarchical levels are equivalent across tasks
  - Task assumptions are correct (ie you have correctly identified processes)
- Task difficulty plays a major role in parametric assumptions
  - More difficult tasks engage the brain more, including in primary regions, and unequally across brain regions
  - Assume equivalent difficulty of all experimental AND all control tasks
-

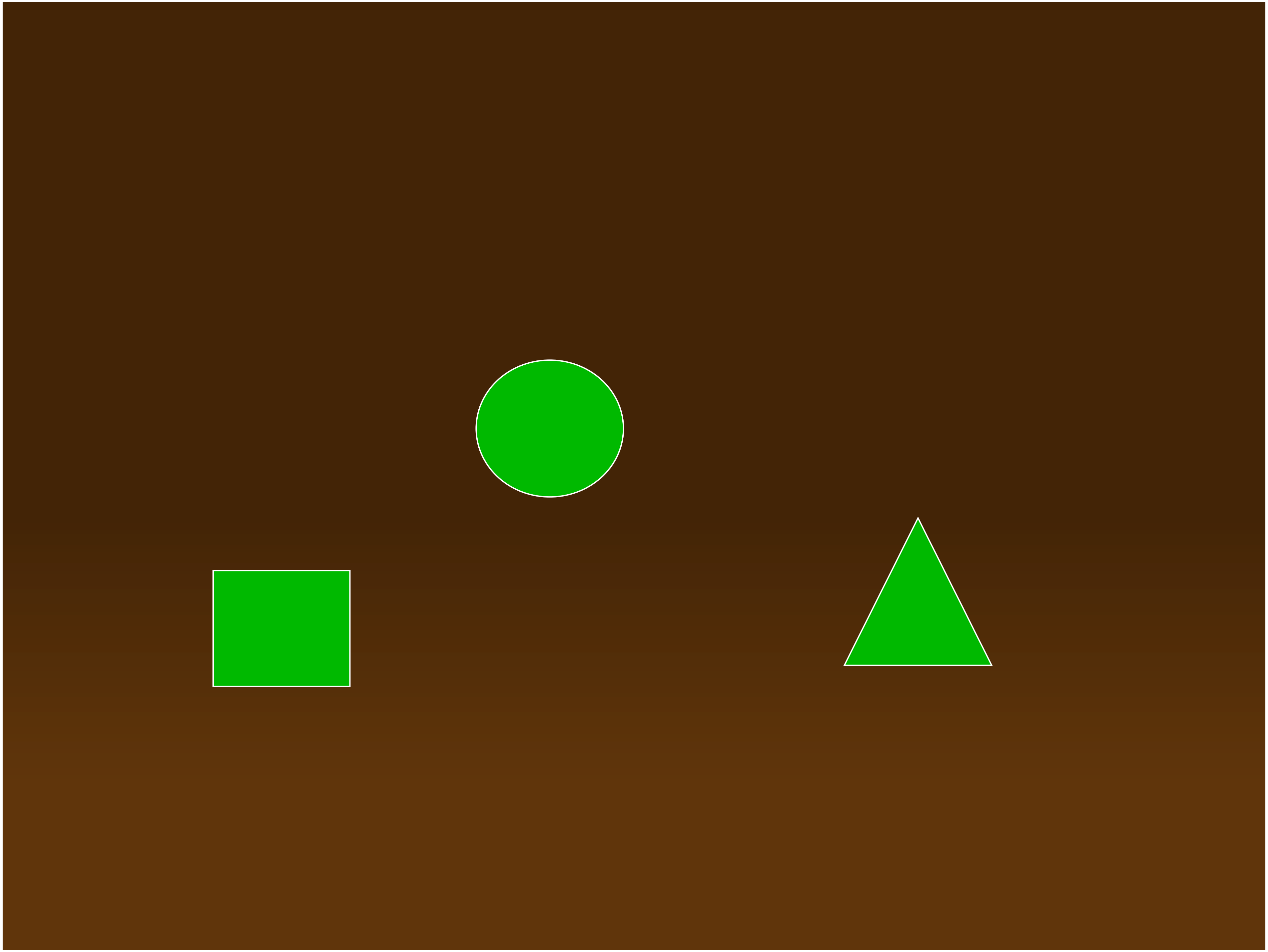
Directed Attention Models

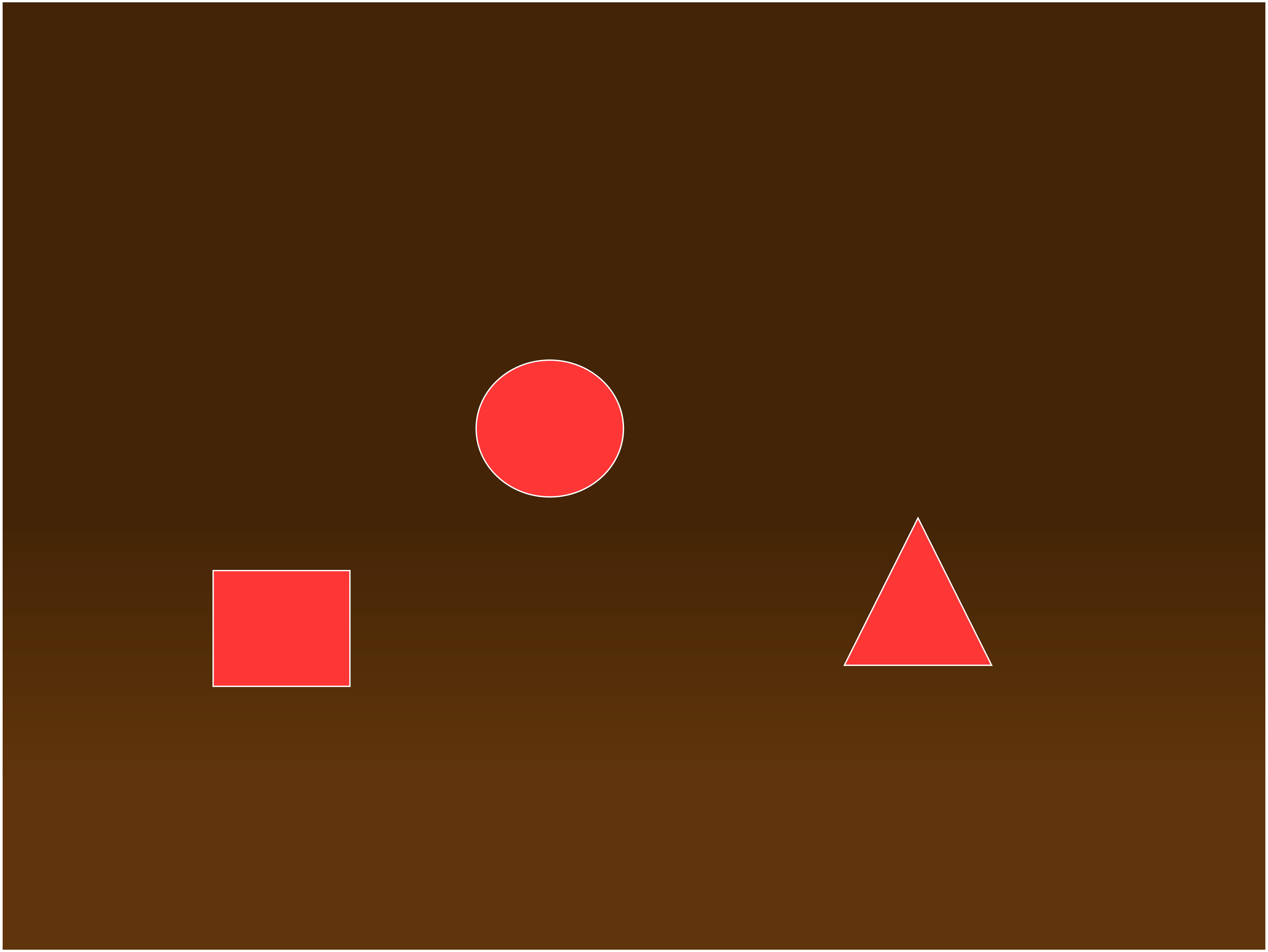
- All stimuli identical in all conditions
- Direct attention towards different features

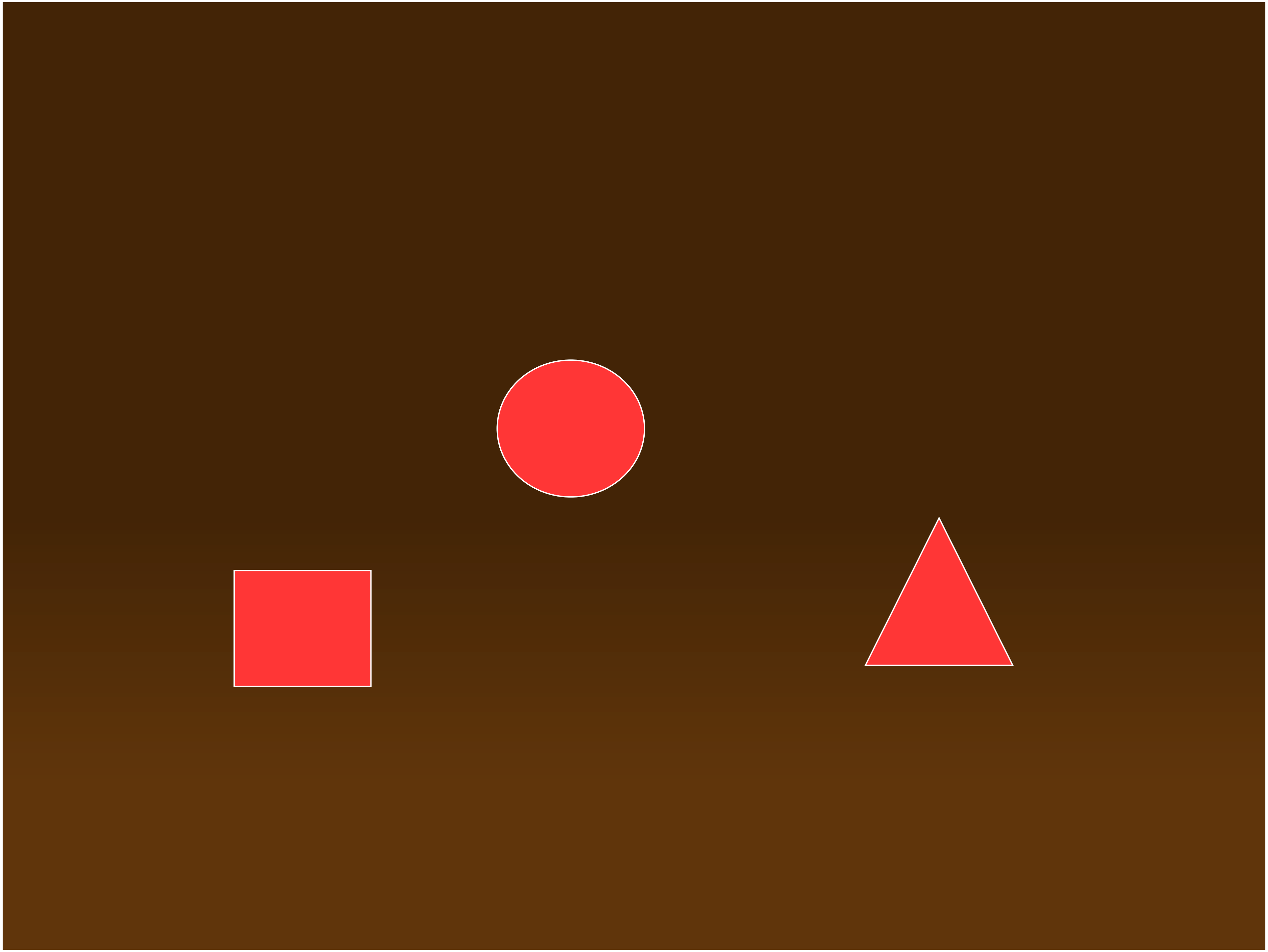
1	**A**	B	C
2	A	**B**	C
3	A	B	**C**

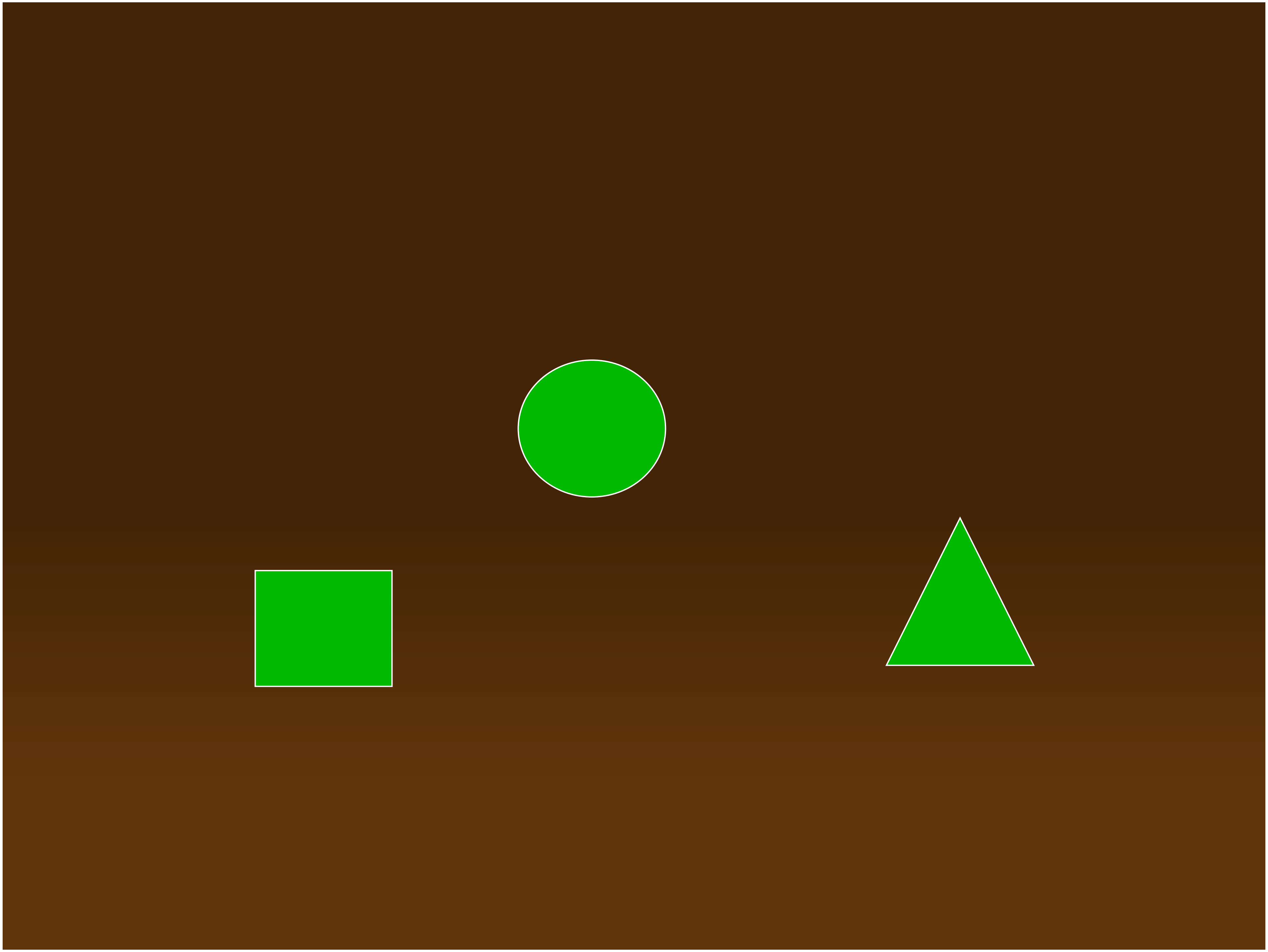
EG Corbetta et al

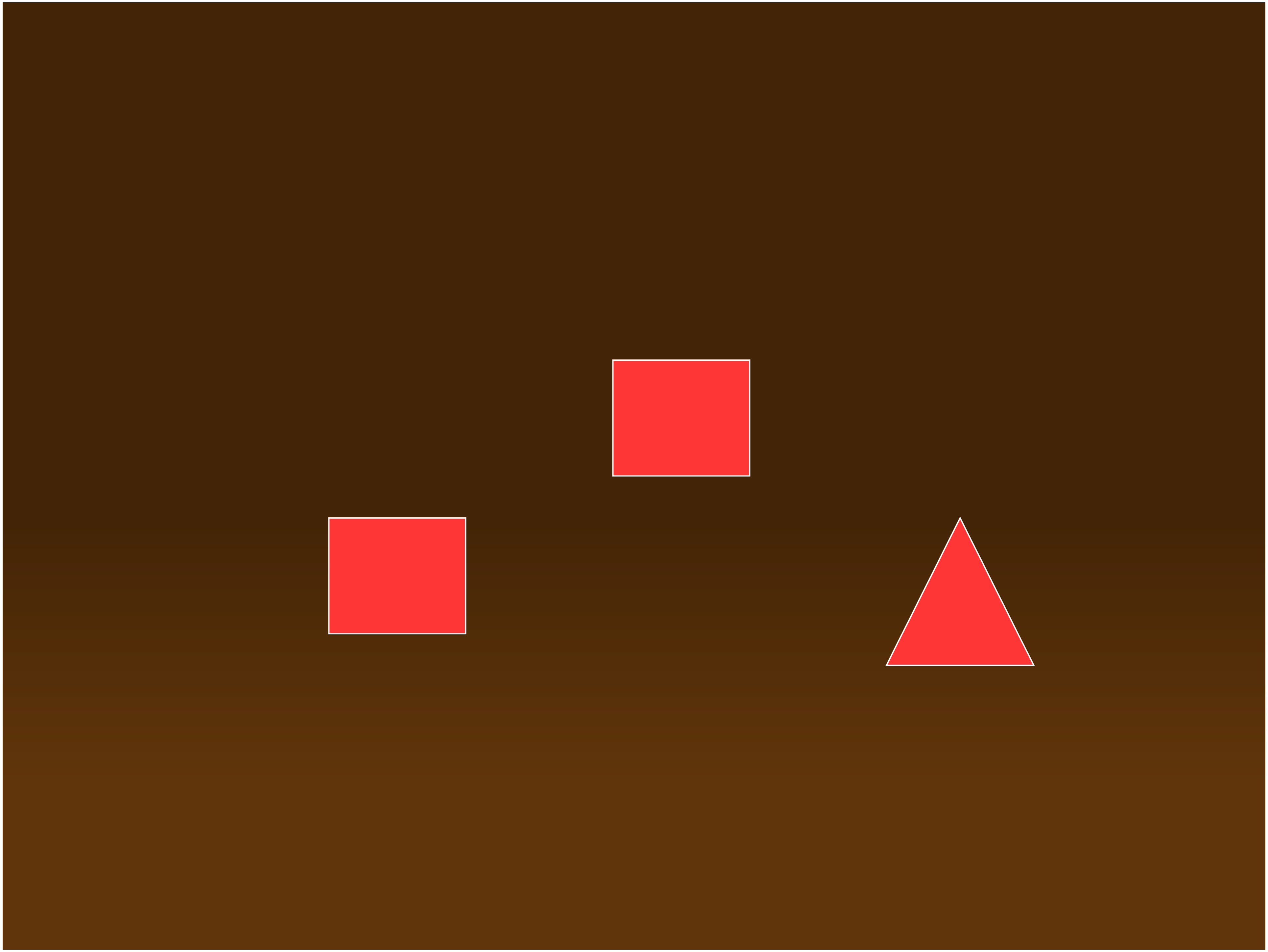
- Identifying separate regions for color, form and motion processing in the visual system
- In every condition, all three variables change
- Told to respond to a shape, color or movement change in different blocks
- Selectively activates form, color, motion centers











Selective (directed) attention designs

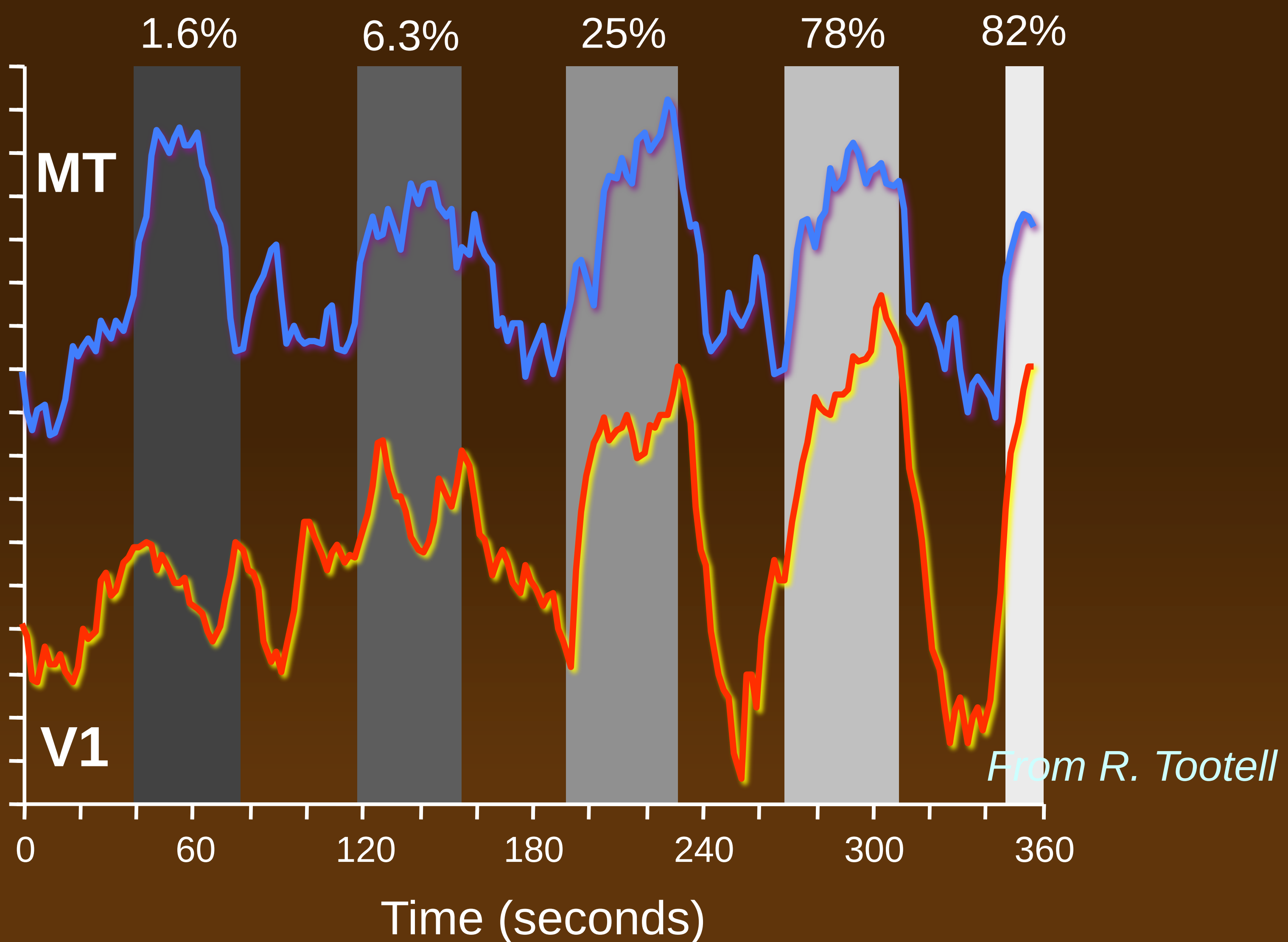
- Implicit or explicit
- Assume process is modified by directed attention
- Assume passive processing does not capture your variable of interest

Parametric designs

- Employs continuous variation in a stimulus/task parameter
  - E.g., working memory load, stimulus contrast
- Inference:
  - Modulation of activity reflects sensitivity to the modulated parameter

A< A < A < A

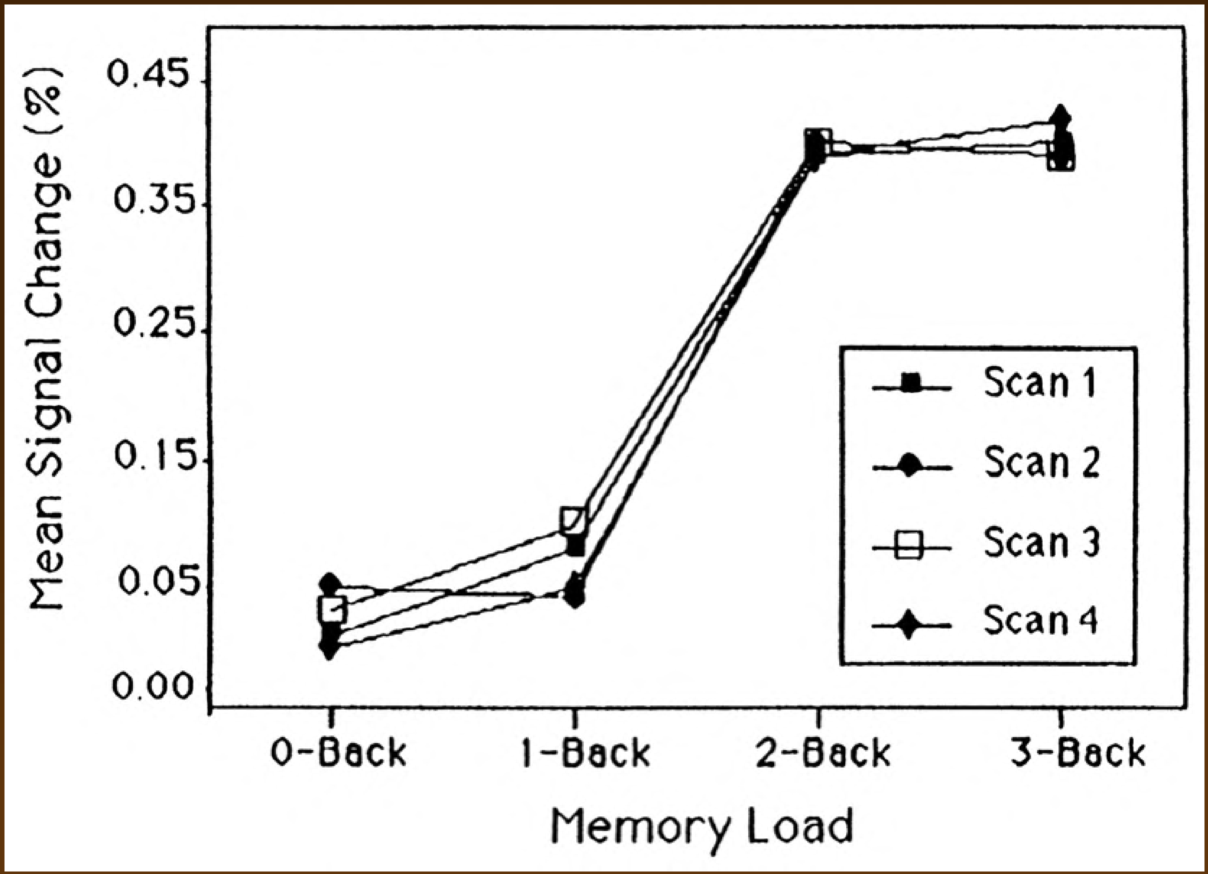
Contrast Response Test



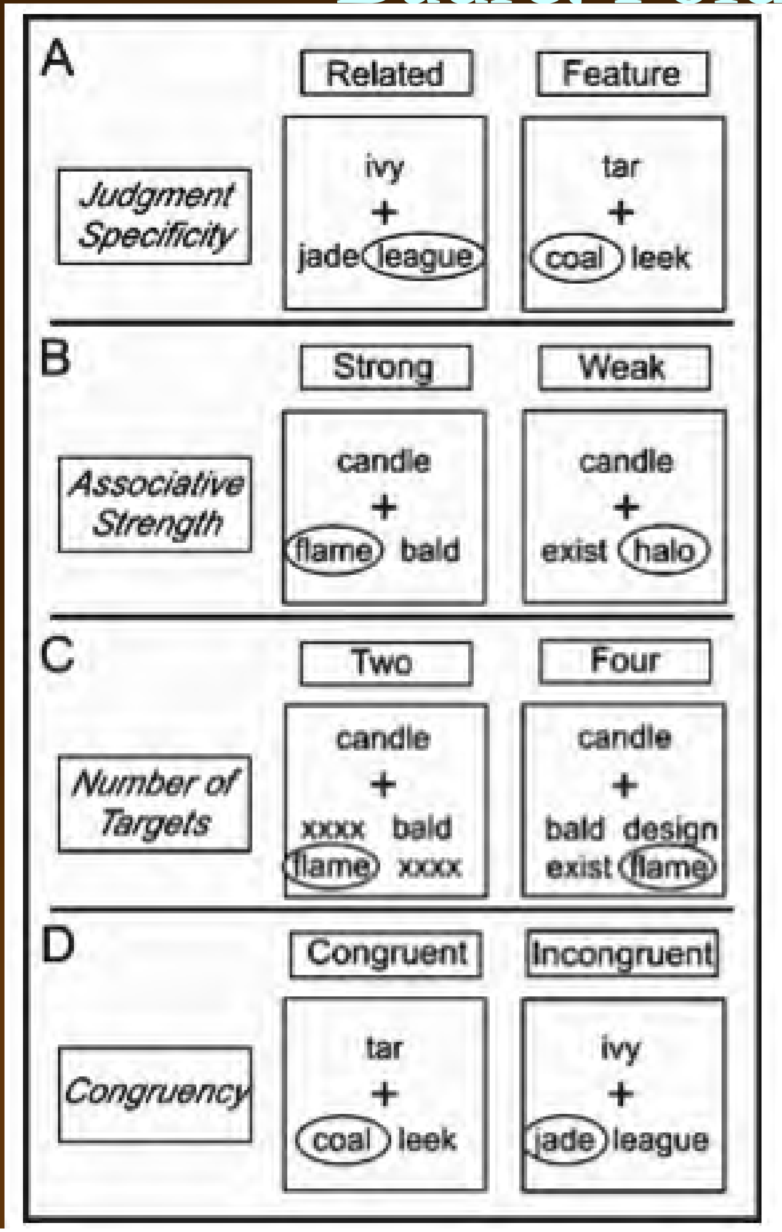
Assumptions of parametric designs

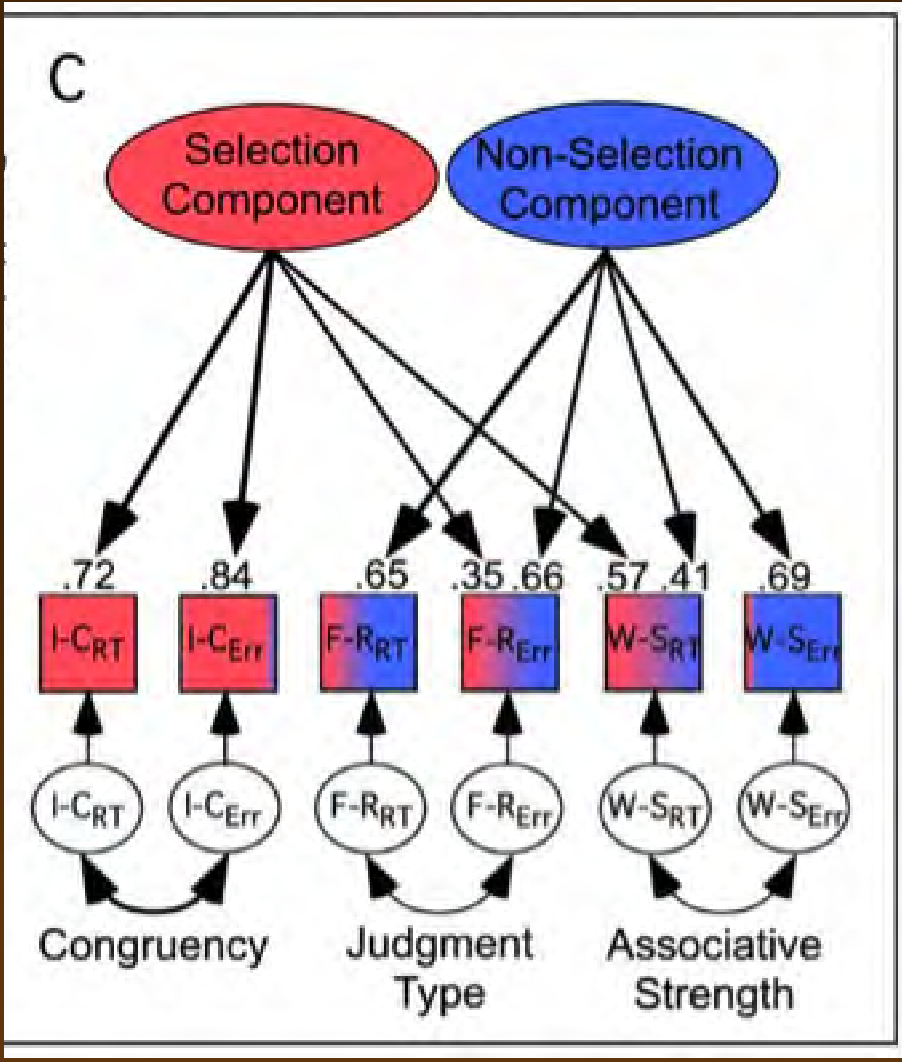
- Pros: you don’t have to design a control conidtion- no subtraction
- Assumption of pure modulation
  - Each level of the task differs quantitatively in the level of engagement of the process of interest, rather than qualitatively
  - Assumes you can define the magnitude differences across levels (usually assumes equality, but not necessarily
- Failures:
  - Response is a step function
  - There are different processes engaged at different levels

Cohen et al., 1996

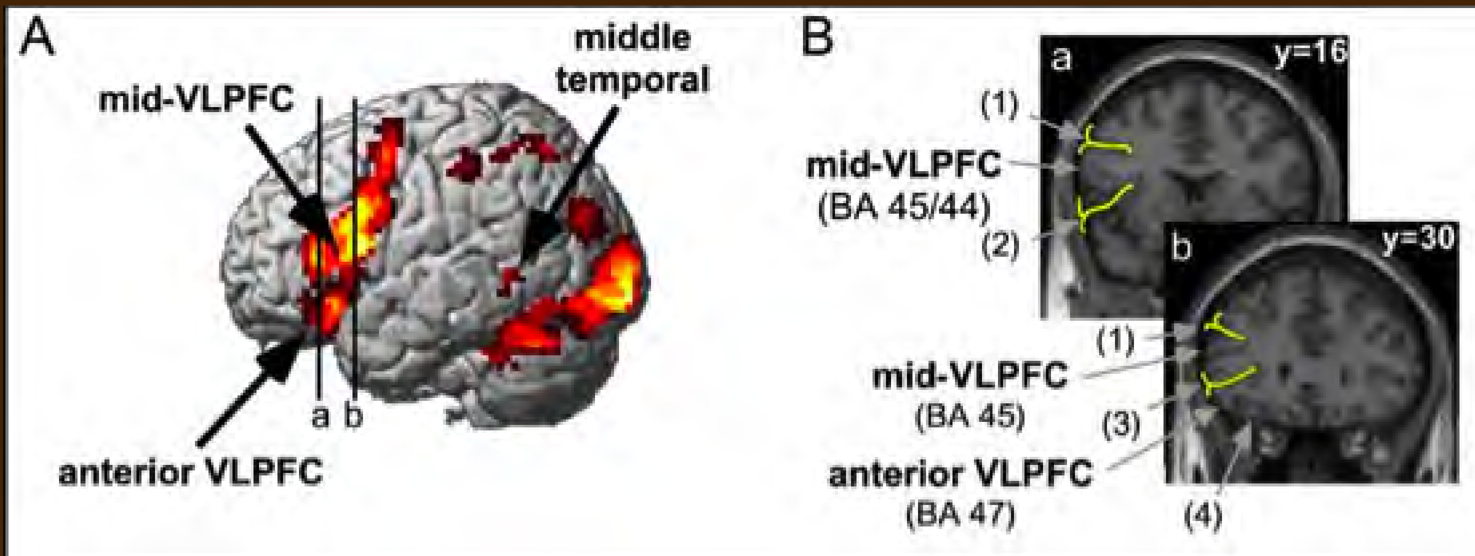


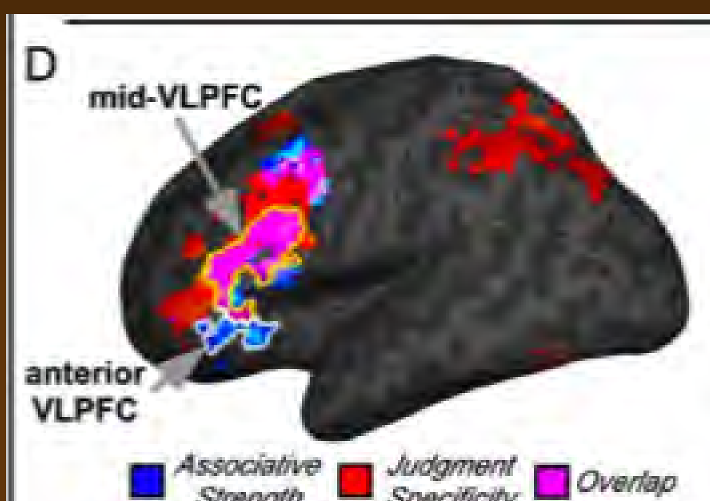
Factor-determined component classification: Badre, Poldrack et al 2005





IFG dissociations





Badre, Poldrack etc 2005

Priming/adaptation designs

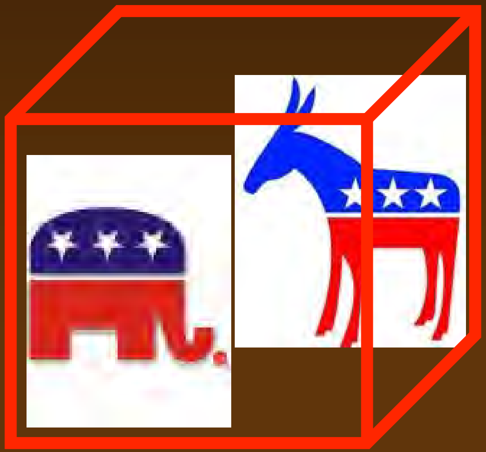
- Presentation of an item multiple times leads to changes in activity
  - Usually decreased activity upon repetition
- Inference:
  - Regions showing decreased activity are sensitive to (i.e. represent) whatever stimulus features were repeated
- Requires version of pure modulation assumption
  - Assumes that processing of specific features is reduced but that the task is otherwise qualitatively the same

Can adaptation fMRI characterize neural representations?

Two stimuli: can neurons tell the difference?

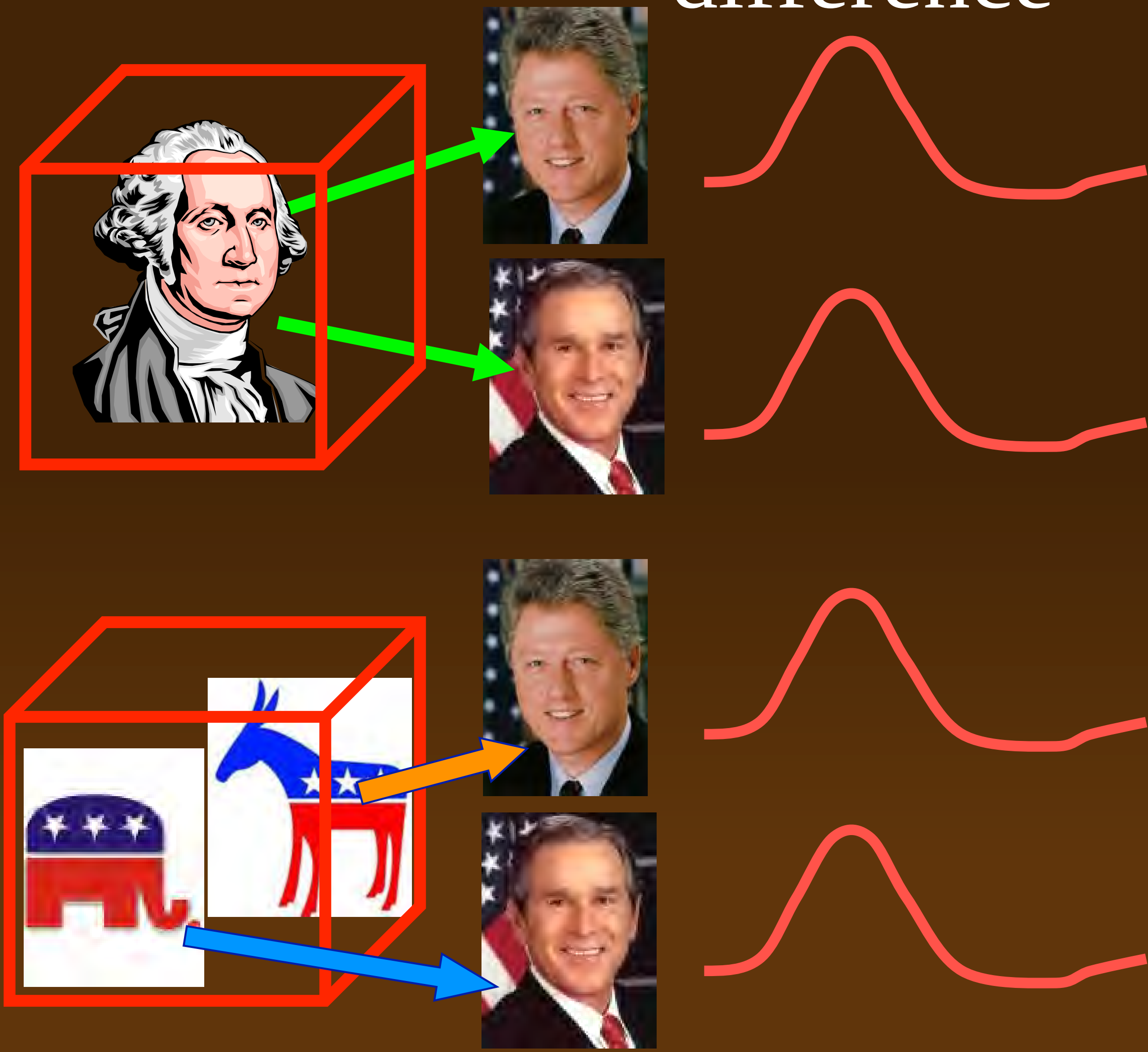
- A voxel containing neurons that respond to all politicians, irrespective of party

- A voxel containing some specifically Democratic neurons, and other specifically Republican neurons.



From R. Raizada

Responses to individual stimuli do not show whether neurons can tell the difference



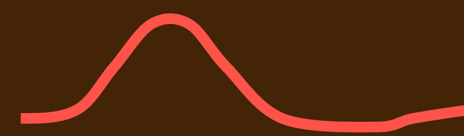
- Different sets of neurons are active within the voxel, but overall fMRI responses are indistinguishable

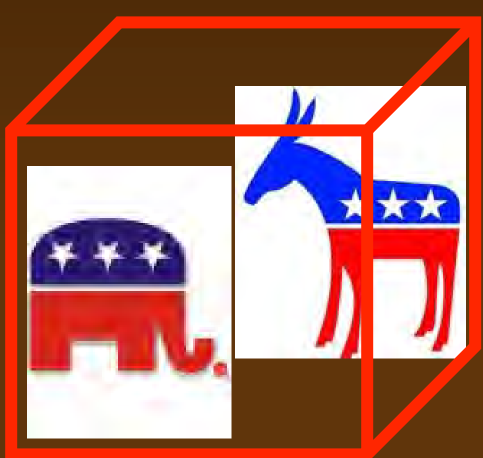
From R. Raizada

Neural adaptation to repeated stimuli does show the difference:
What counts as repetition for neurons in a voxel?


It’s a politician

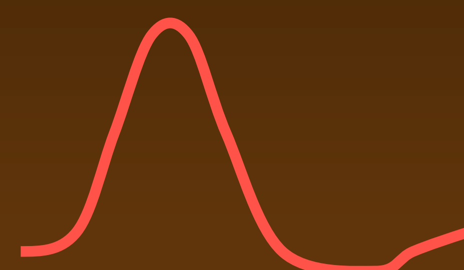
Same neurons, adapting:
It’s a politician again






It’s a Republican

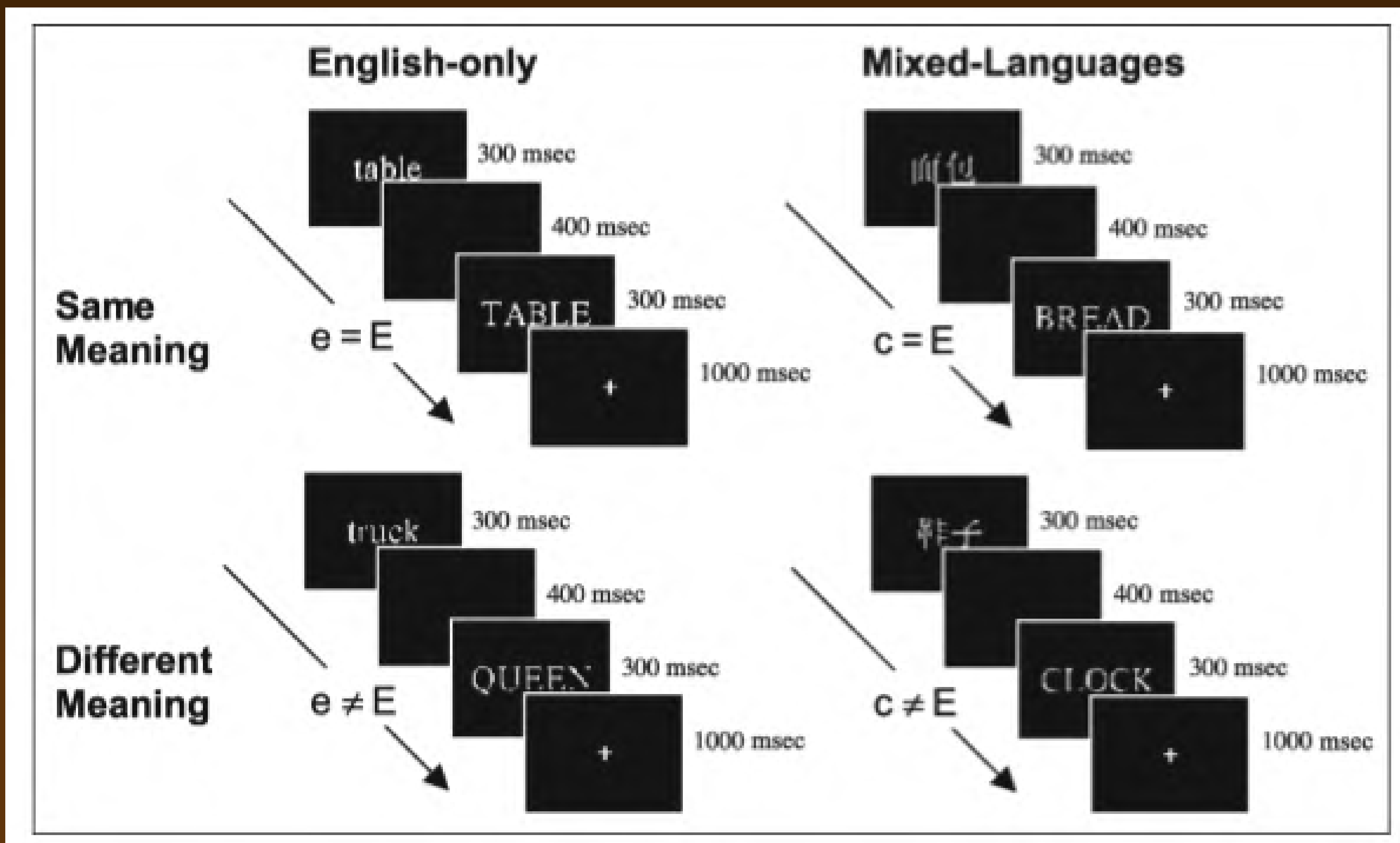
Different, fresh neurons:
It’s a Democrat



From R. Raizada

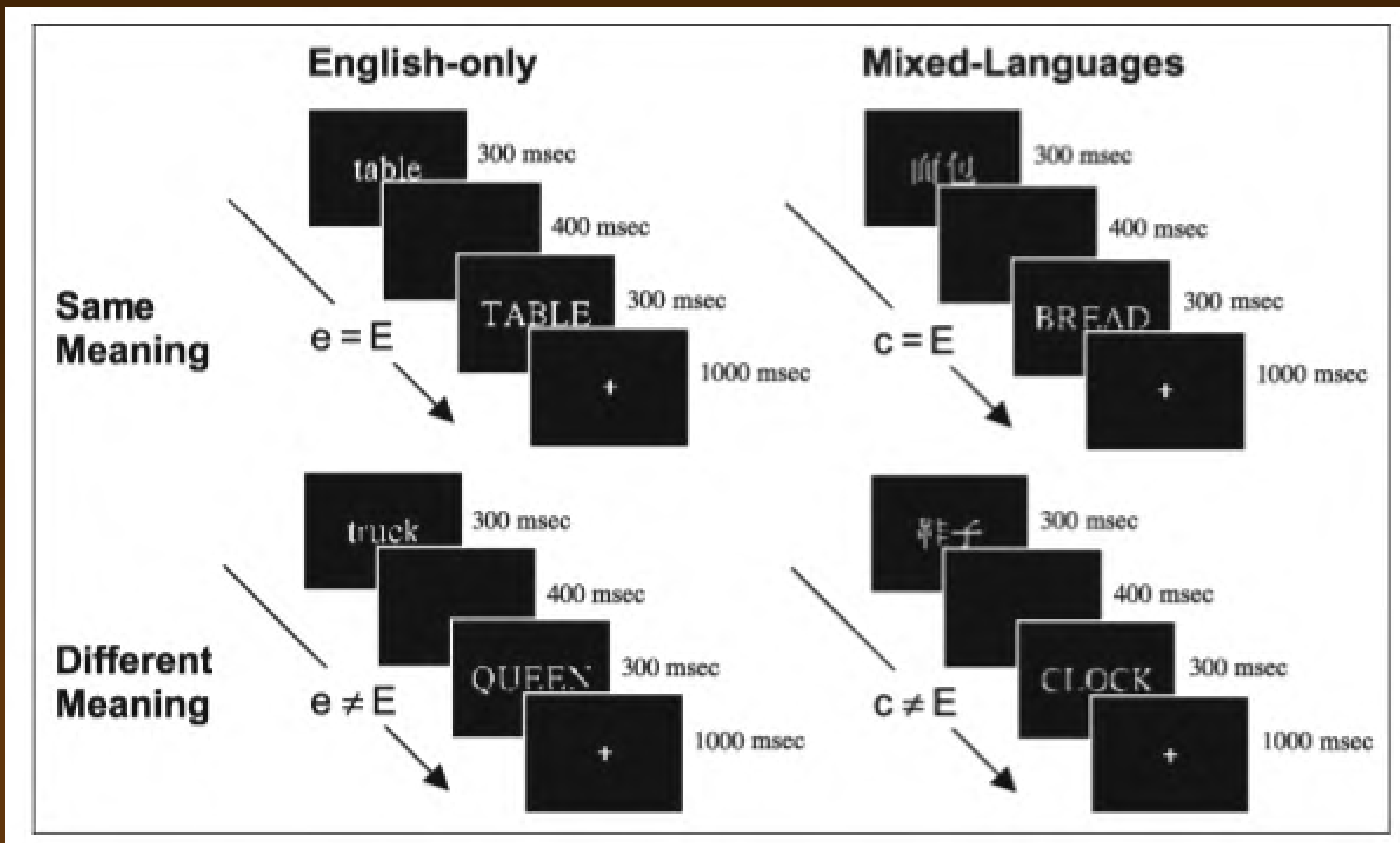
Adaptation in bilingual subjects

Do different language share semantic representations across languages in bilingual subjects? Chee et al



Adaptation in bilingual subjects

Do different language share semantic representations across languages in bilingual subjects? Chee et al



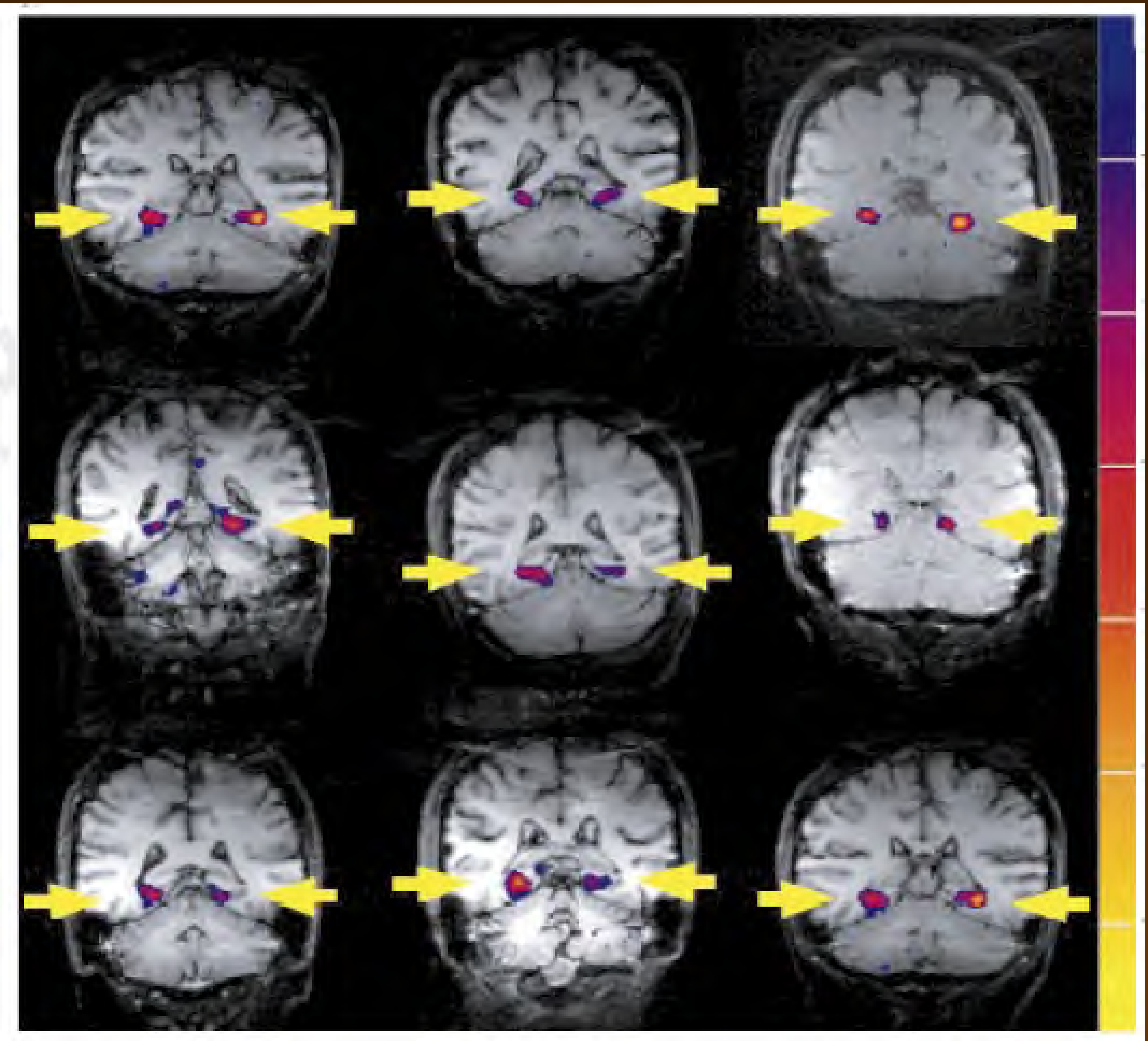
The functional characterization approach

- Many studies take a “functional mapping” approach
  - The final goal is to say that area X is active in relation to process A
- Another approach is to first identify an area of interest
  - Often based on a subtraction design, along with other knowledge from neuroscience
- Then, use multiple task manipulations to characterize the function of the area

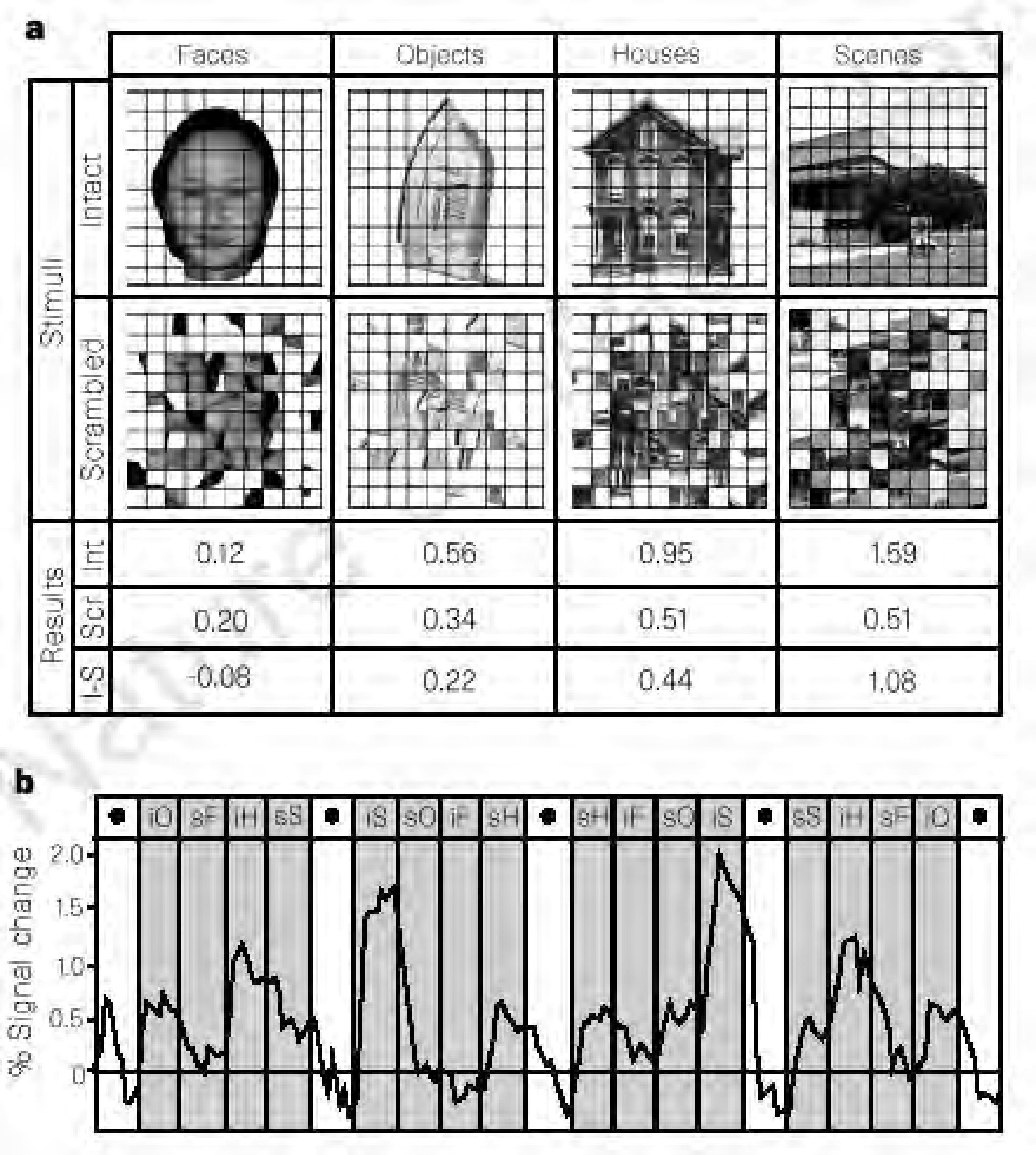
Parahippocampal place area (Epstein and Kanwisher 1998)

- Blocks: Faces, objects, houses, scenes
- Intact and scrambled
- Analysis:
  - ROIs = pixels in target area **from an independent scan**
  - Compute signal diff for scram. vs. intact
  - Diff sig > for scenes than for others
- Alternatives and control exp.s
  - Can you think of other alternatives or controls?

Epstein et al: Localizer



Epstein et al: Functional characterization



Conjunction analysis (Price & Friston, 1997)

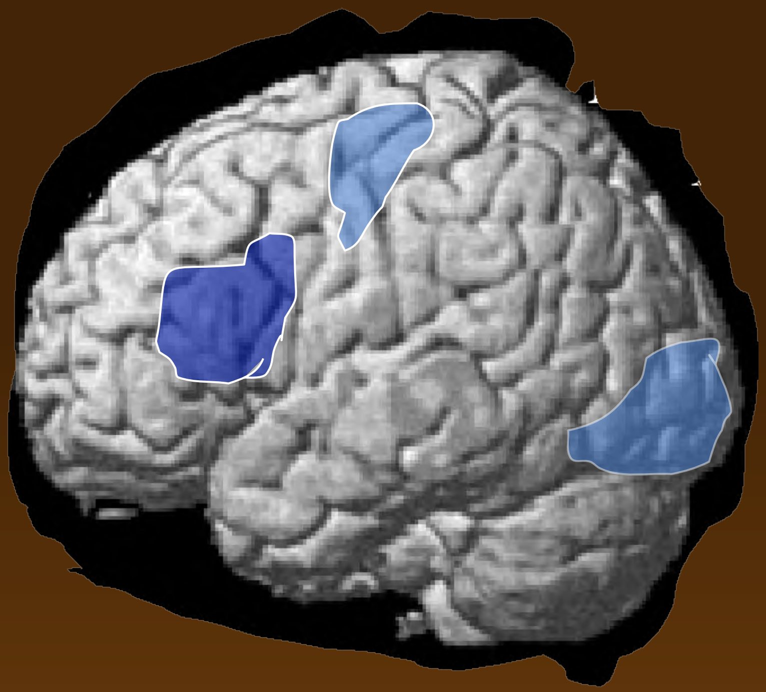
- Perform several parallel subtractions
  - Each of which isolates only the process of interest
- Find regions that show common activation across all of these

Conjunction Analysis

Ex A - Ctl

Ex B - Ctl

Ex C - Ctl

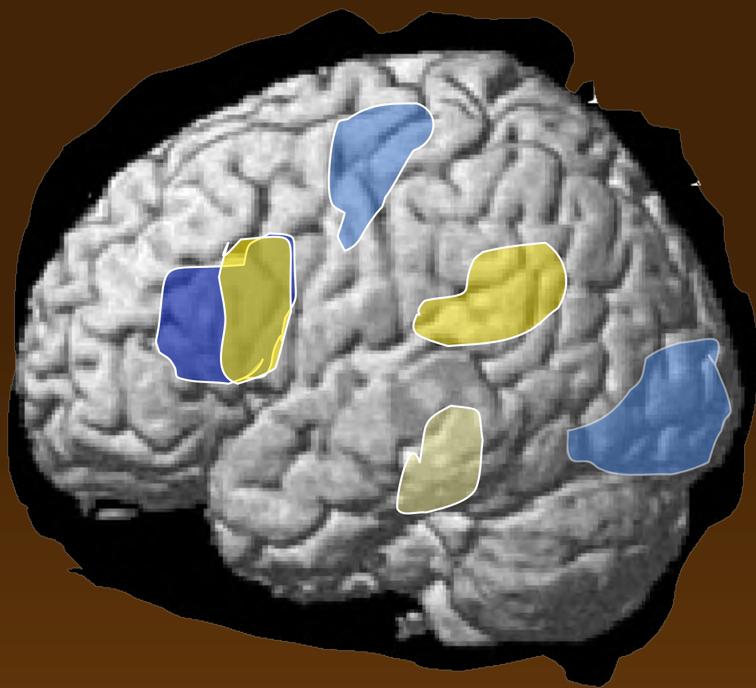


Conjunction Analysis

Ex A - Ctl

Ex B - Ctl

Ex C - Ctl

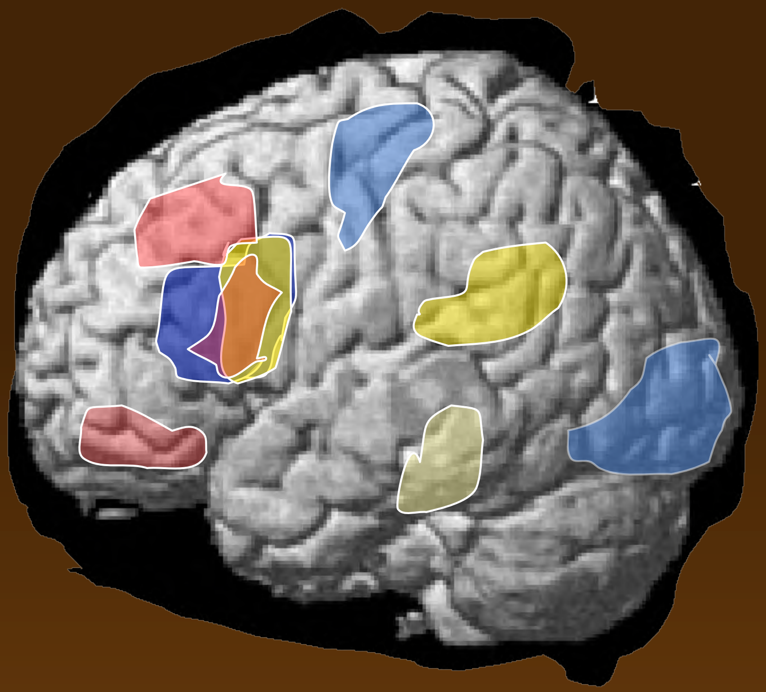


Conjunction Analysis

Ex A - Ctl

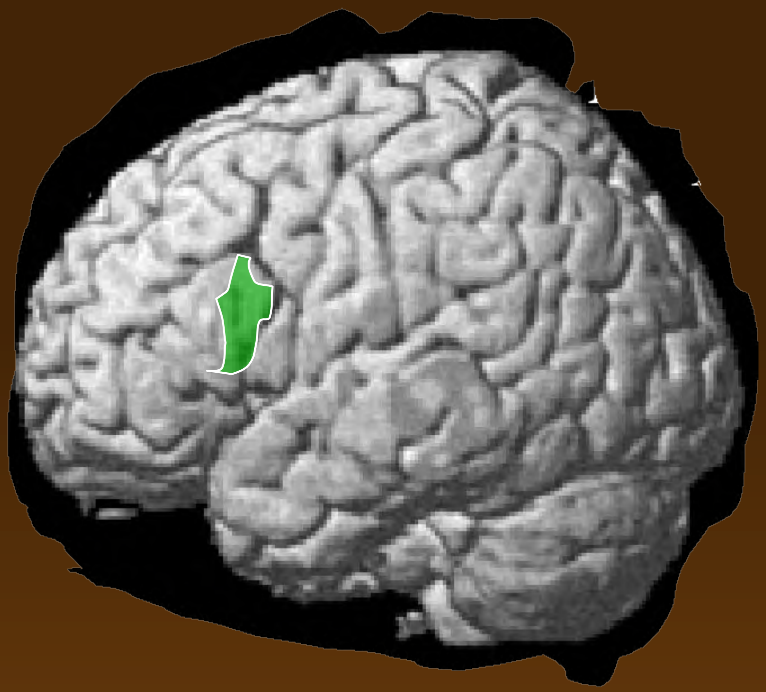
Ex B - Ctl

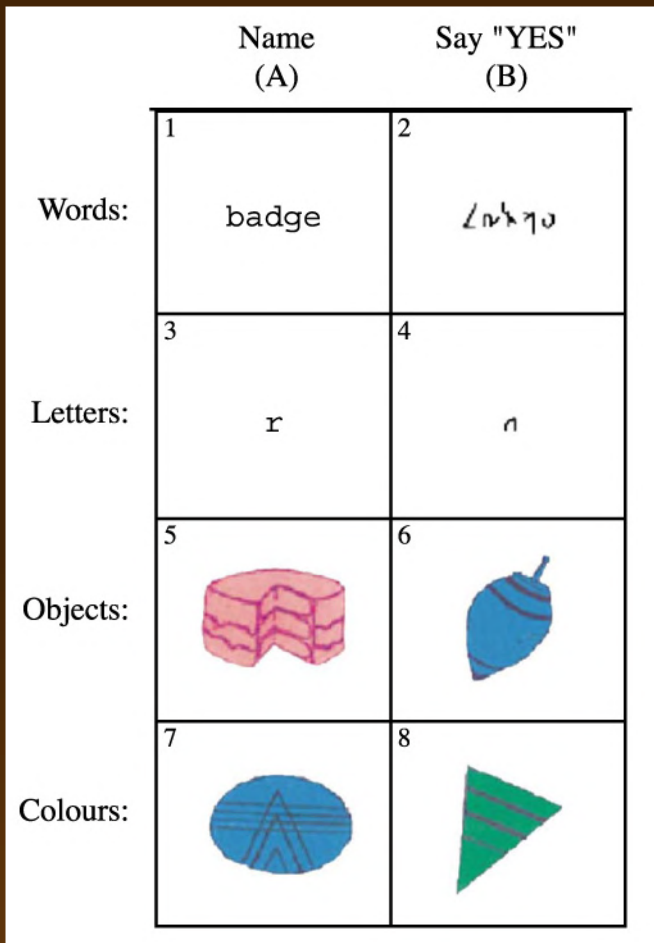
Ex C - Ctl

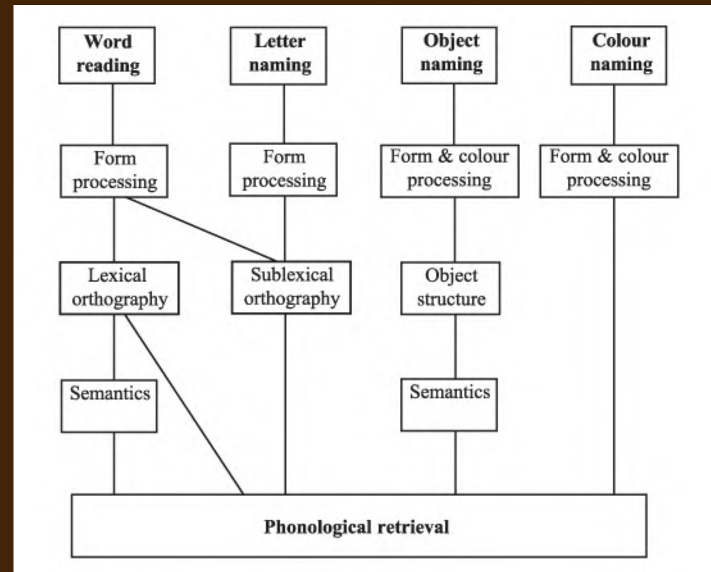


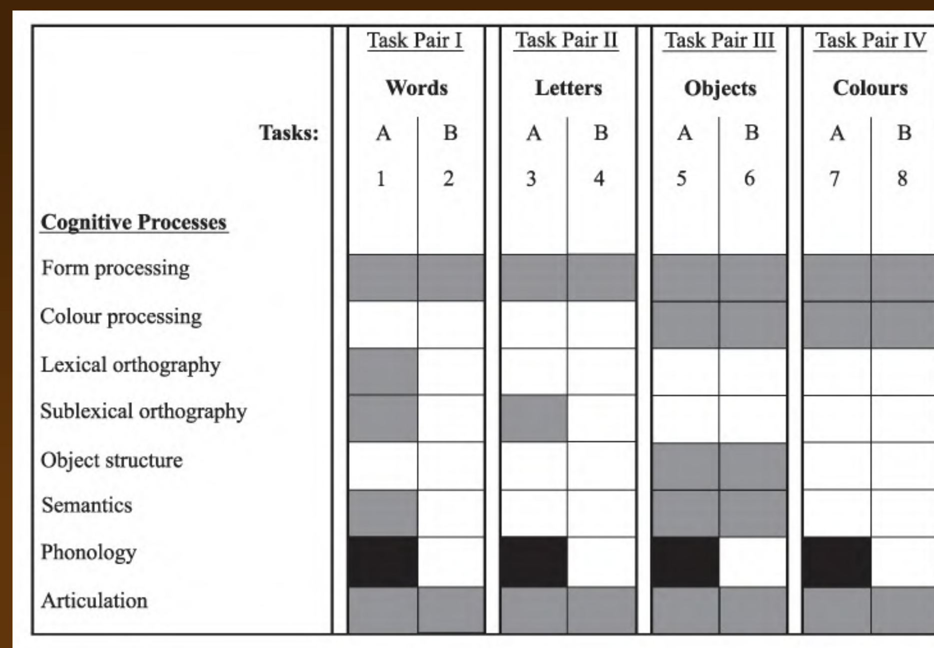
Conjunction Analysis

A AND
B AND
C



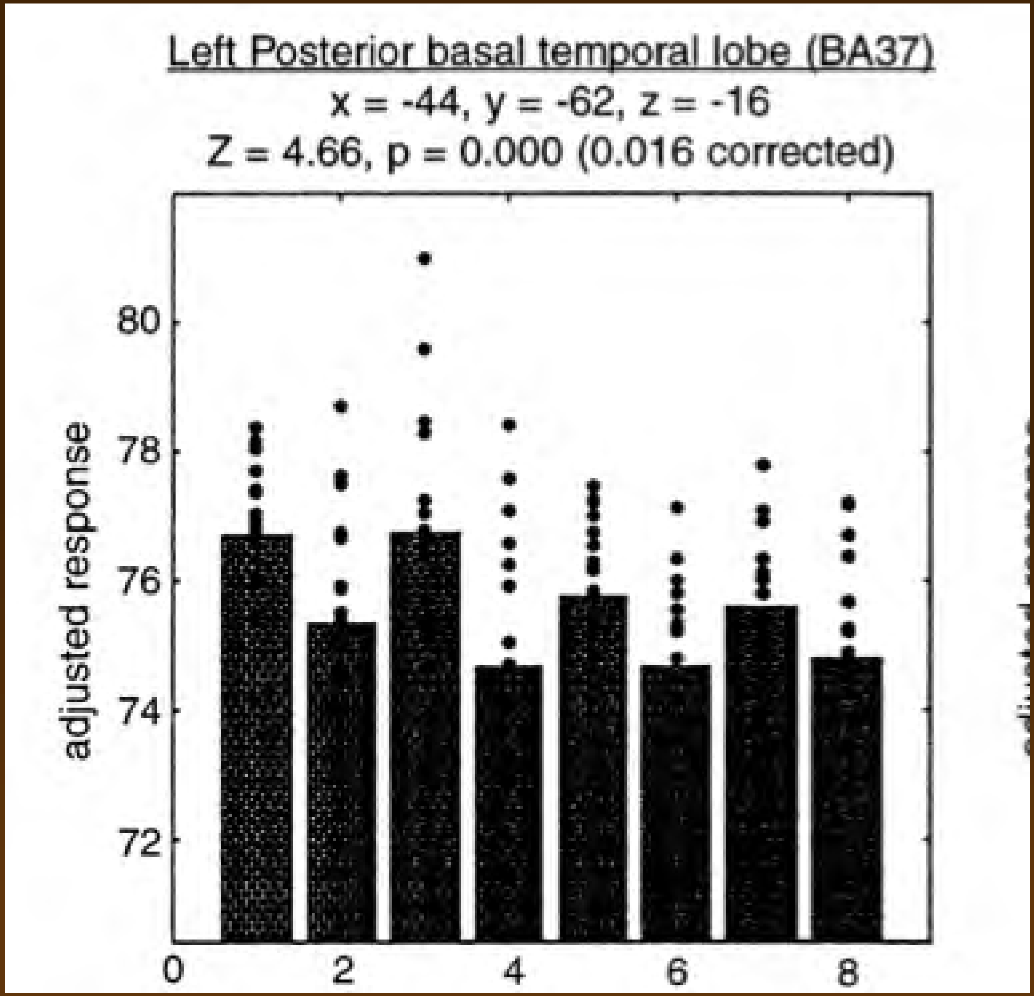






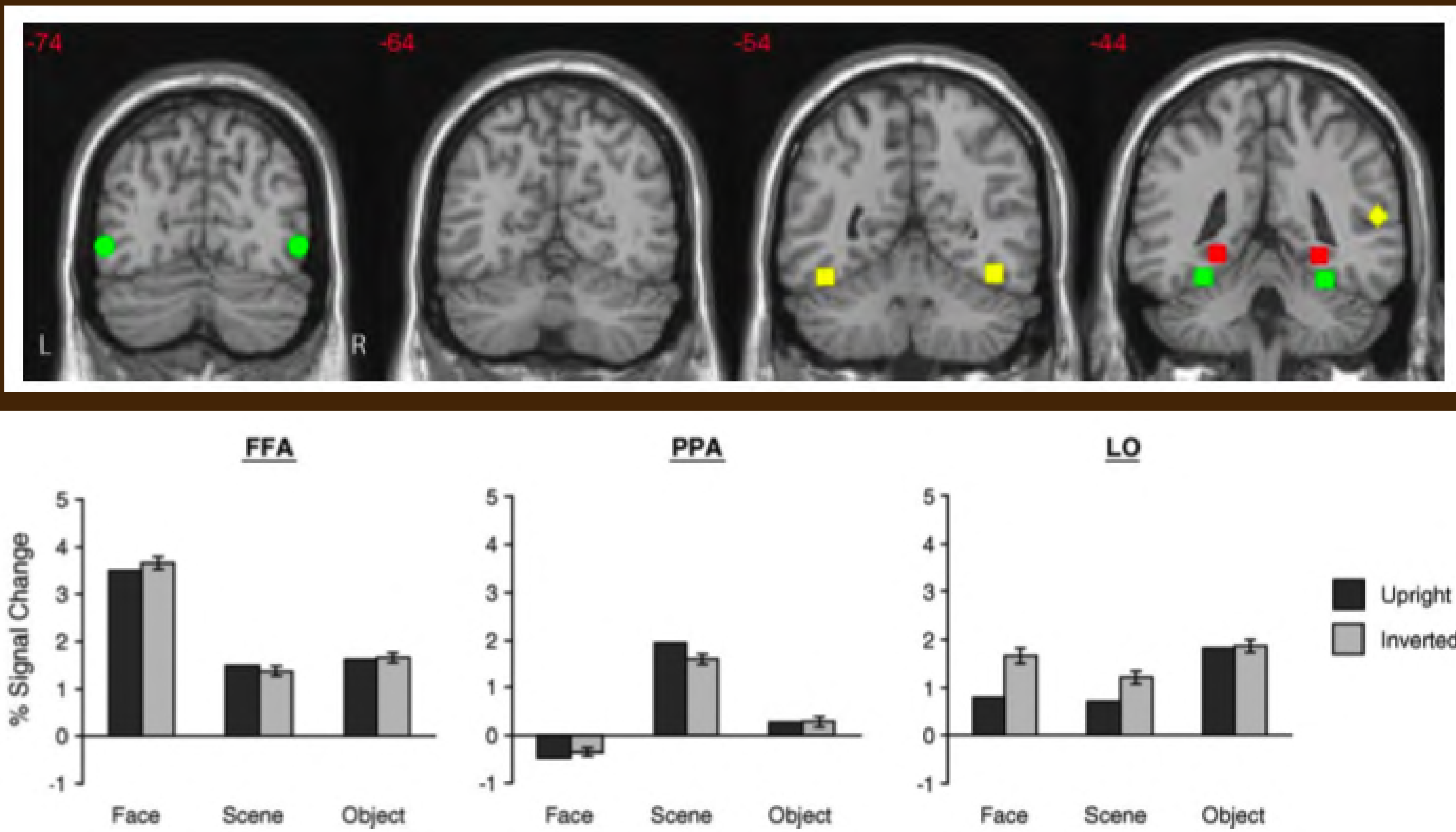
from Price & Friston, 1997

BTLA- all tasks involving accessing phonology



Problems with conjunction analysis (Caplan & Moo, 2003)

- Many assumptions about what processes are involved
- Implicit processing
  - Subjects may engage processes that are not necessary for the task- does not measure magnitude differences
- Interactions between processing stages
  - Conjunction only gets rid of interactions if they do not activate the same regions to the same degree across tasks
- We use this approach for finding consistent but low-level activations in clinical mapping



-74
-64
-54
-44
L
R
FFA
PPA
LO
% Signal Change
5
4
3
2
1
0
-1
Face
Scene
Object
Upright
Inverted

Counterbalancing

- With more than 2 conditions- essential
- EG: Low, medium and high stress conditions
  - Habituation
  - Order effects eg High carry-over
- Complete counterbalancing (recruit in groups of N! where N is the total number of conditions)
  - 1 2 3 132 231 213 312 312
- Latin Square (recruit in groups of N conditions)
  - 123 231 312
  - Each condition in each serial order
  - **assumes no task-task order interactions**

2-group designs

- Build on any of the prior designs
- Additional between group comparisons
- Hypothesis sounds something like: the differences between experimental and control task in my patient group differs from that difference in controls
- Assumes baseline task performance is equal

Summary

- No design is perfect; all make assumptions that are not fully verifiable; know them!
- Use that which is most consistent with your specific research question; freely admit weaknesses
- Avoid reverse inferences- have a hypothesis before you begin
- Multiple “baseline” conditions help interpretation
- Beware of your assumptions
-