
NeuroImaging
Training
Program

Experimental Design for Imaging I

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Conceptual and methodological aspects of experimental design

- There are two aspects of fMRI design that are important to distinguish
- Conceptual design
  - What neuroscience question are you trying to answer?
  - How do we design tasks and control conditions to properly measure the processes of interest?
  - The issues here are very similar to those in cognitive psychology
- Methodological design
  - How might these psychological variables map onto blood flow changes in the brain
  - How do we can we construct paradigm 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; our job is to understand, justify, and test these assumptions, using the best design for our question
- The logic involved and choosing tasks and contrasting them, and the problems of assumptions in these choices, spans all experimental designs
- In this context, it makes no difference whether we use event related or blocked designs, eg. "Null" events in ER designs often = "rest" in block designs.

Some experimental questions

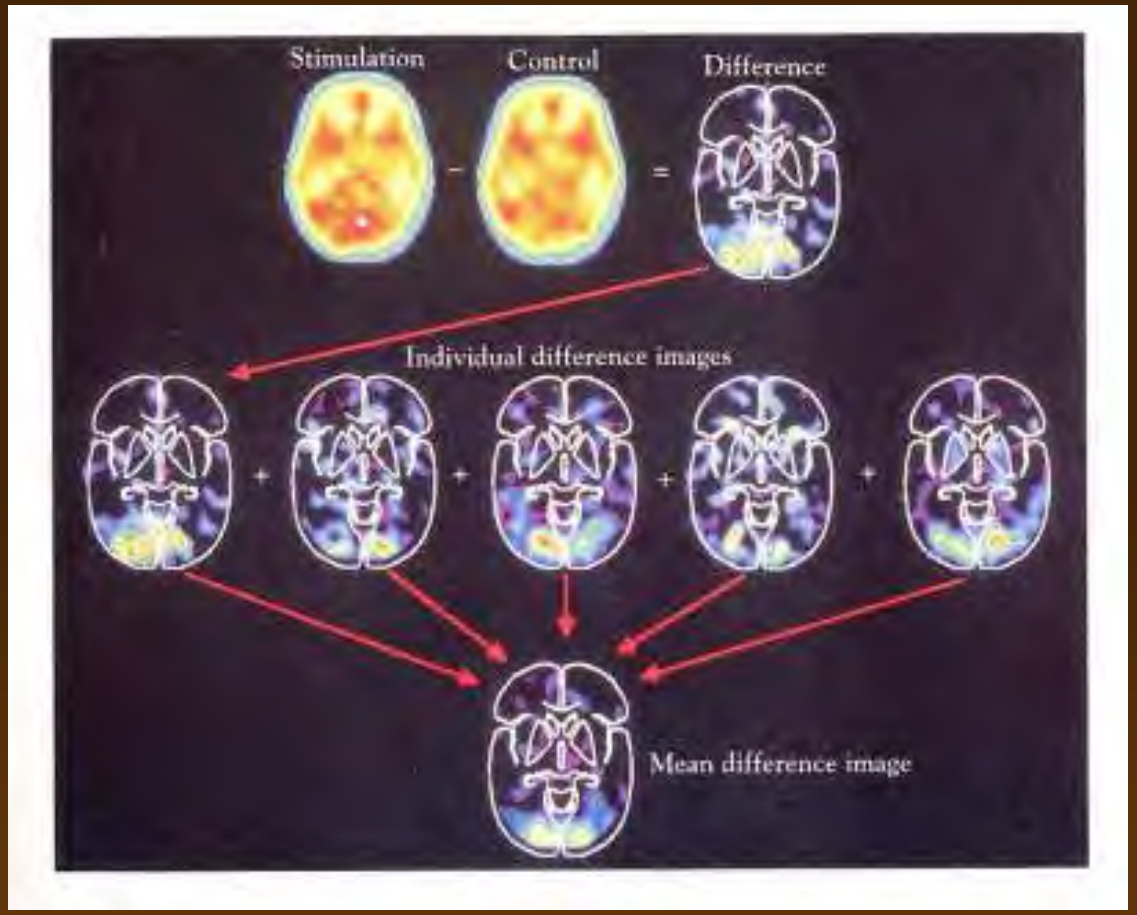
- What brain areas are active when we perform a task of interest?
- What is the nature of a specific aspect of information processing in a brain region “activated” by a task?
- What is the nature of the computation performed in a brain region
- How do different individuals (groups) vary in the networks engaged in a specific task
- Questions related to connectivity- different lecture

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
- Experimental Task Increase 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.

The task analysis assumption

- Subtraction assumes that the task analysis is correct
  - No other processes are implicitly engaged by the baseline task
- Example 1: What regions within the language network are specific for semantic processing?
- Language task: Subjects see a printed word
  - Experimental “semantic” condition- generate a verb from the printed word
  - Control “word naming”: read the presented word
  - E-C= semantic processing, because C did not require semantics, only reading
  - Controls for visual activity: see 1 word
  - Controls for motor activity: respond by producing a single word
- What are our assumptions? How might they go wrong?

Task Analysis Assumption

- Example 2: memory
- Question: what areas of the brain are associated with learning (memorizing) a list of words?
  - Experimental Task: See a list of words, instructions to memorize the words
  - Control Task- see a well matched list of words; just read them (or, say whether they have a letter “l” in them
  - Control for visual word processing- only difference is that in one case, subjects are memorizing
  - E-C= memory
- What assumptions are we making? Are they valid?

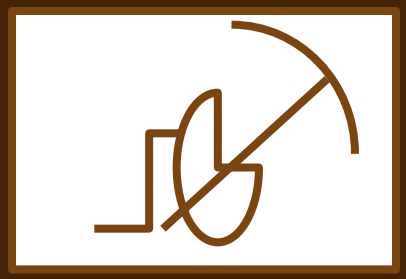
The pure insertion assumption

- 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

Example of pure insertion (additive factors) assumption

What brain regions are specific for Reading words, independent of motor

C1: view shapes



E1/C2: Read Silently

E2: Read aloud

CONTRAST: E1 (silent) – control (shapes) = word processing areas

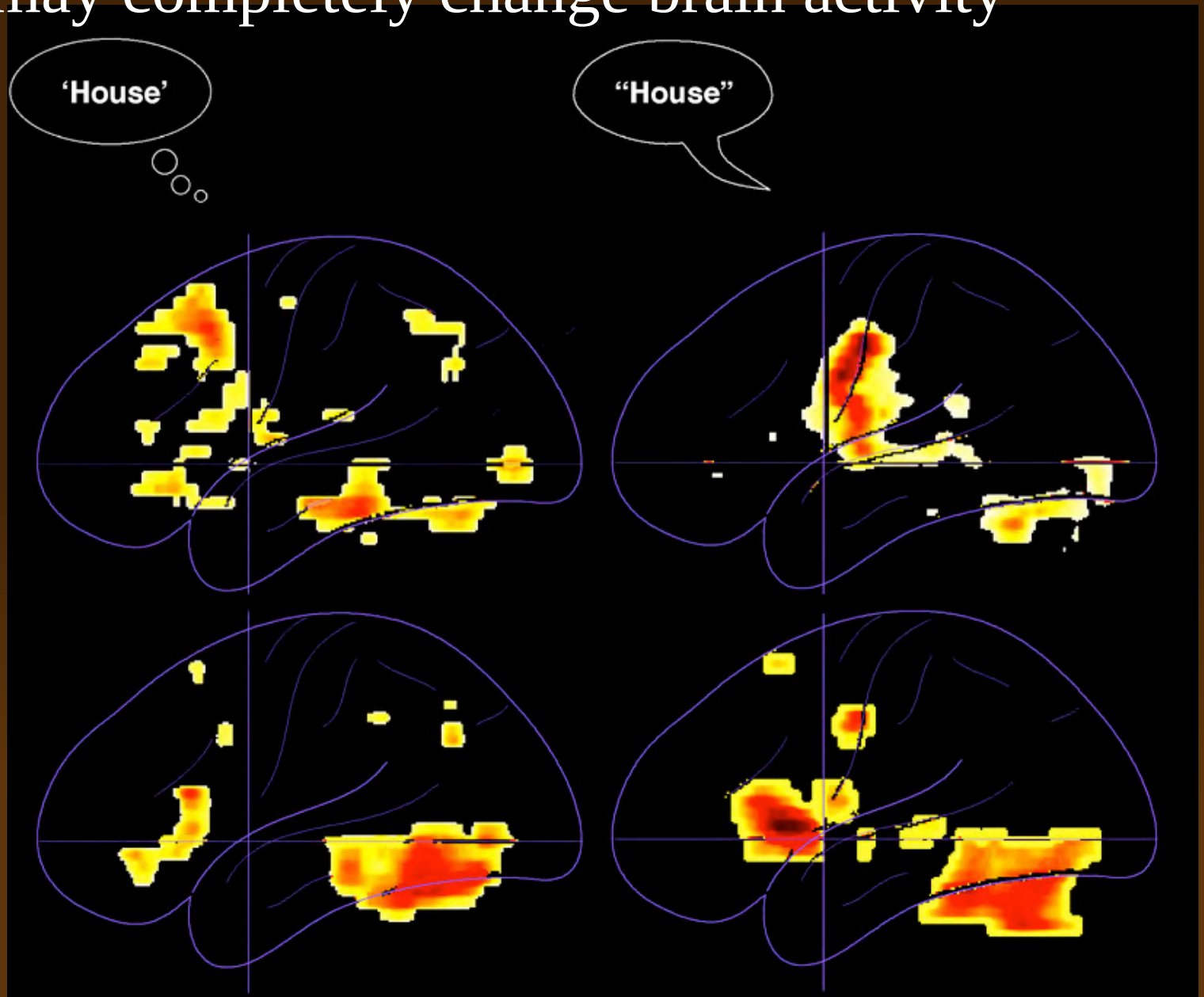
CONTRAST: E2 (aloud) – control (silent) = motor areas

Pure Insertion (additive factors) assumption:
Reading aloud is identical to reading silently EXCEPT the addition of motor ; ie, adding process does not influence the existing process;
reading aloud = reading silently + motor

Answer: Sometimes yes, sometimes no. Adding a process may completely change brain activity

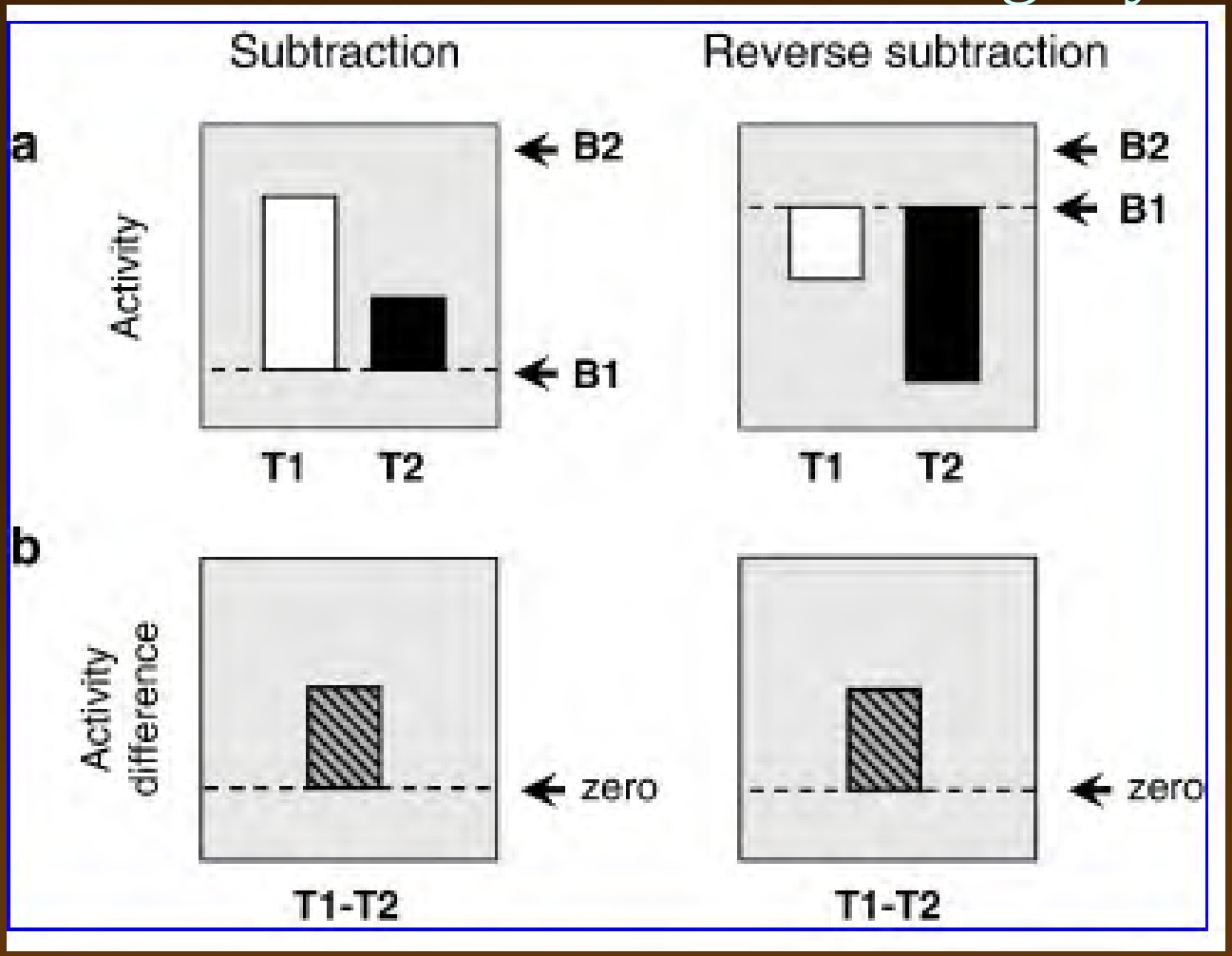
Read
“**HOUSE**”

Name

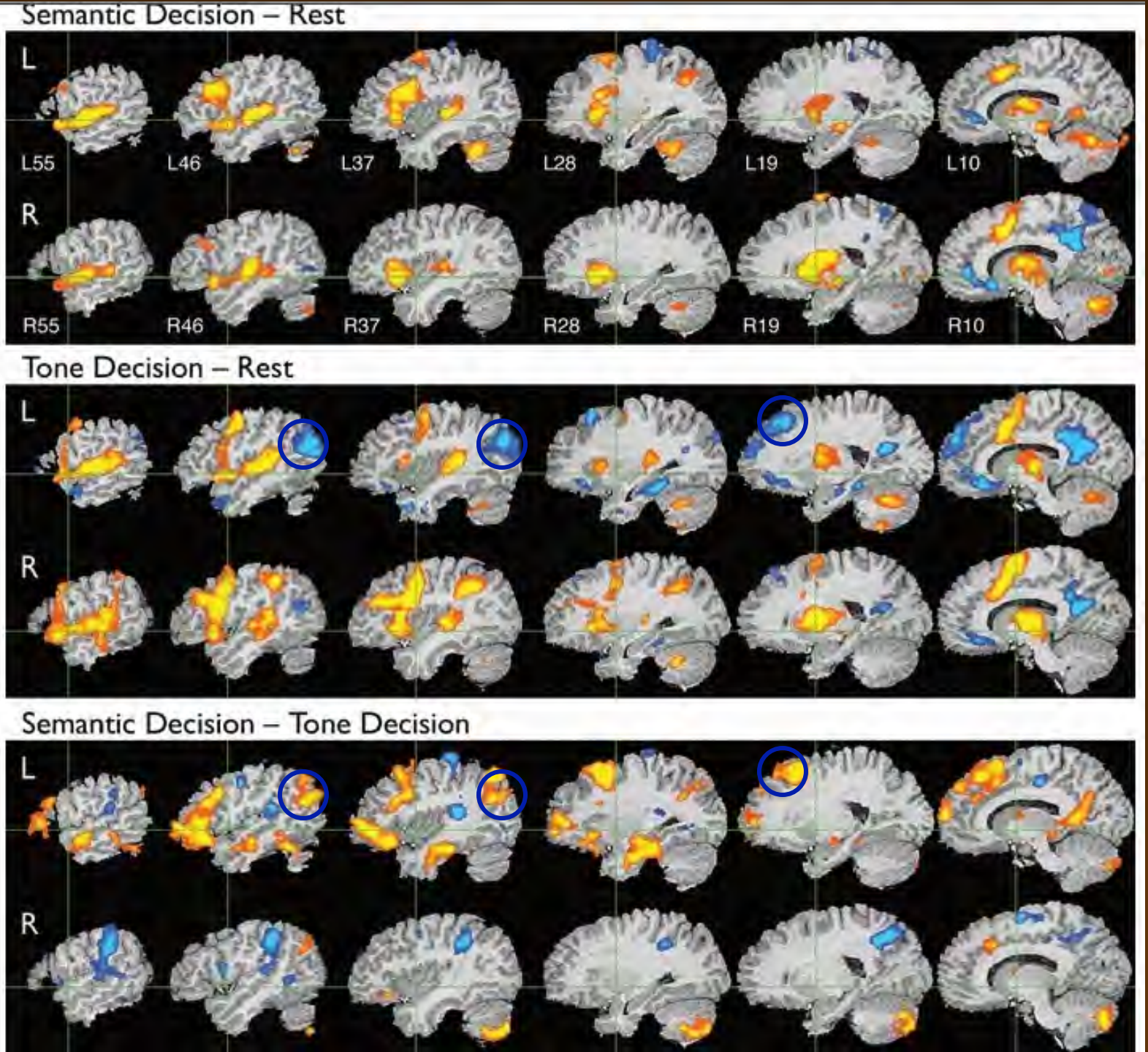


Experimental Increase assumption

"My experimental task minus my baseline shows increased blood flow during my task"



From Morcom and Fletcher, NeuroImage, 2006


Semantic Decision – Rest
L
L55
L46
L37
L28
L19
L10
R
R55
R46
R37
R28
R19
R10
Tone Decision – Rest
L
R
Semantic Decision – Tone Decision
L
R

Subtraction Designs

Simple

Exp Task – Control
= Process of interest

Hierarchical

Ex B
–
Ex A
–
Control

Common baseline

Ex A Ex B

Control

Parallel

Ex B > Ex A

Ex A > Ex B

Tailored Baseline

Ex A > Ctl A

Ex B > Ctl B

>

Hierarchical subtraction

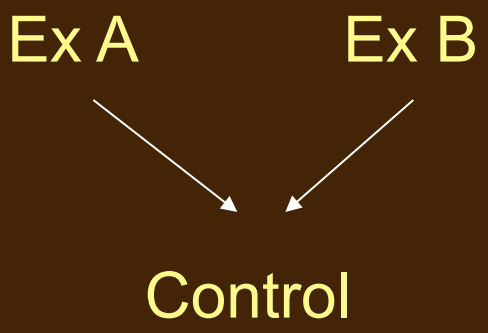
example from Petersen, 1991

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

Strong assumption of pure insertion, at multiple levels:
The more levels of hierarchy, the harder it is to interpret your data

Does passively listening to words activate language areas?

Common Baseline



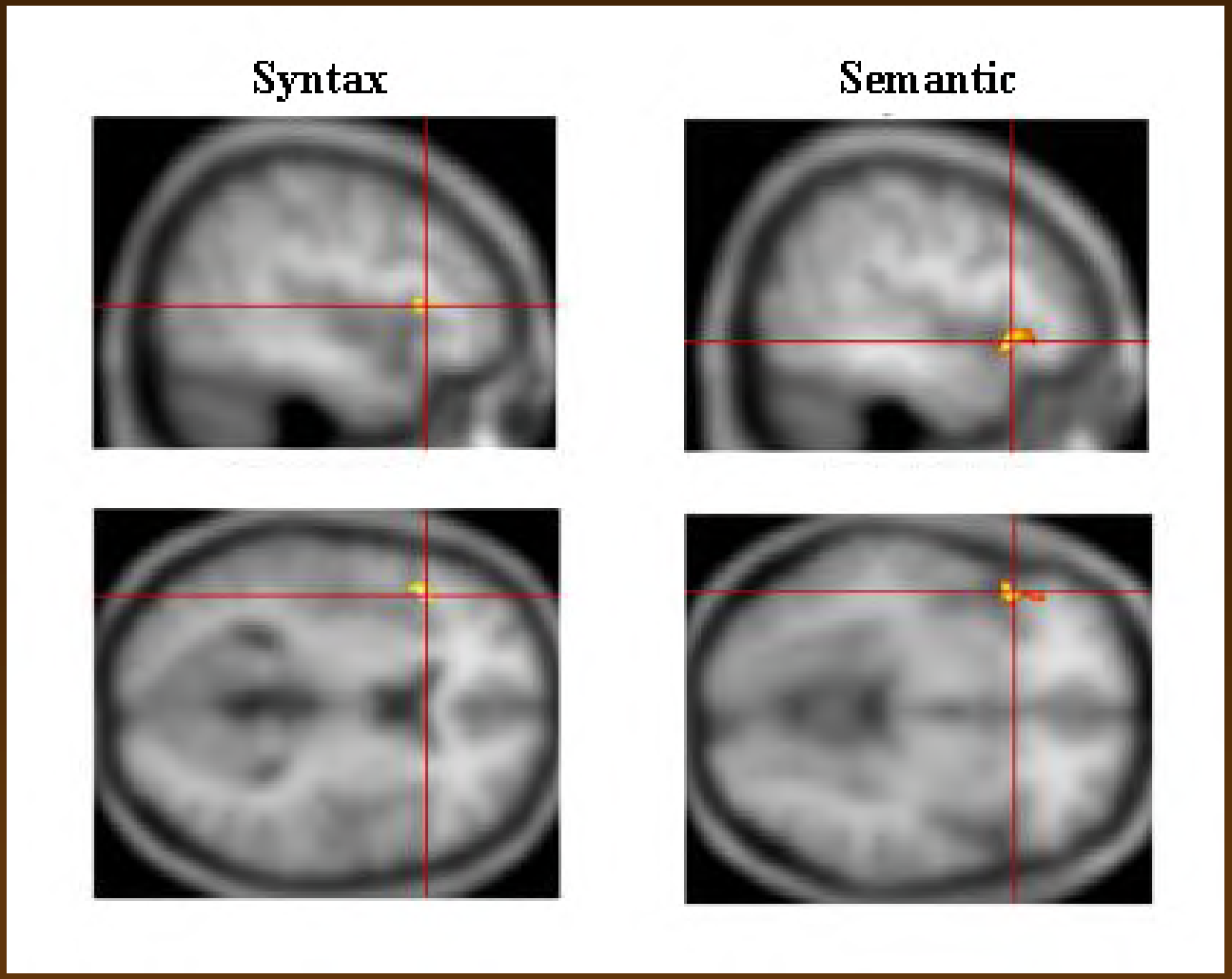
- One level of hierarchy
- Test for violation of additivity assumption
- Allows you to see common areas active for A and B
- Does not test for A vs. B
- Assumes A and B are equally hard, equal variance, etc. ie similar psychometric properties
- Need additional approach to see unique areas to A vs. B

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
  - With multiple baselines, ALWAYS examine each level of comparison

Are there unique divisions within IFG for syntactic vs. semantic aspects of sentence comprehension?
Syntax > Semantics; semantics > syntax



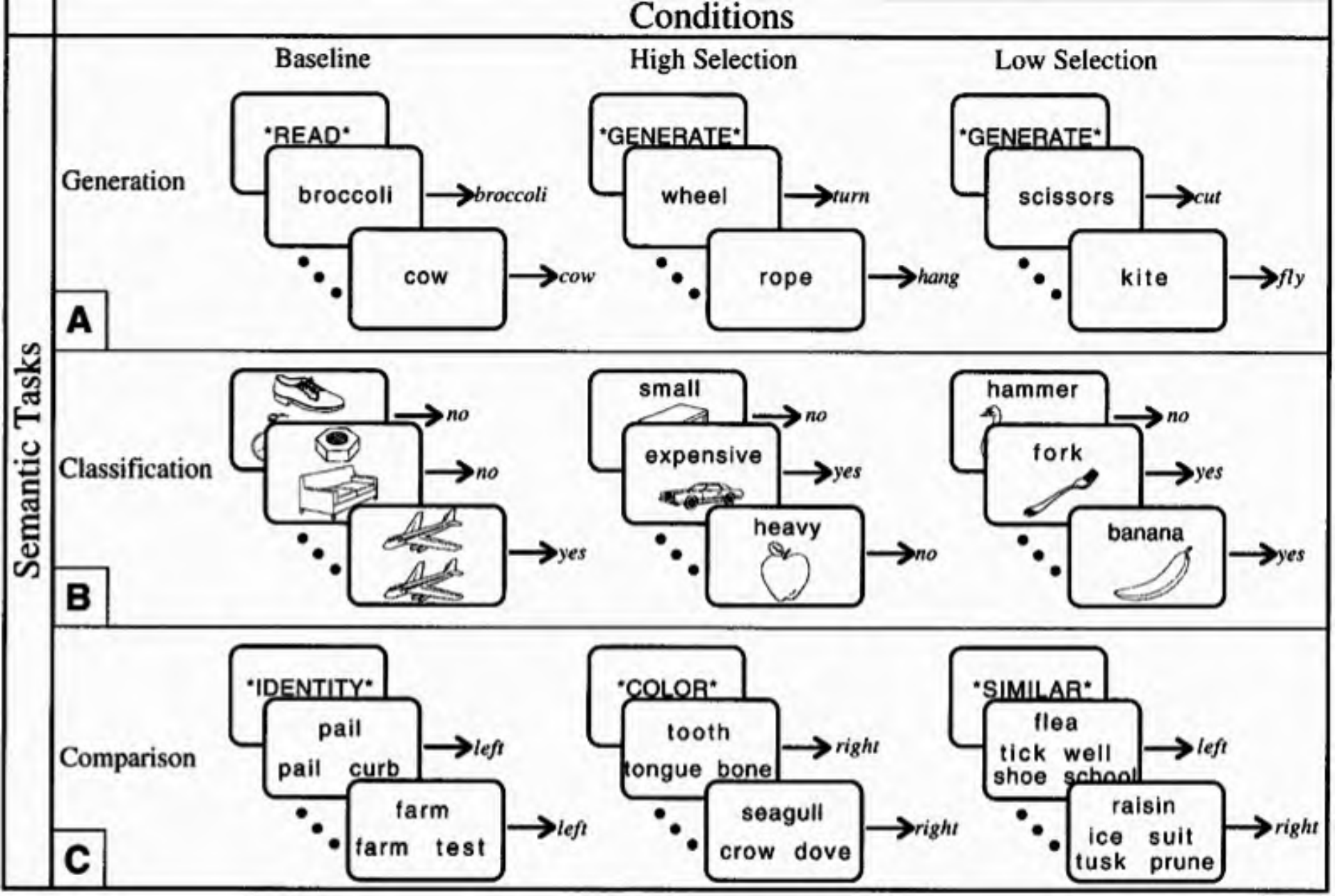
Dapretto and Bookheimer, Neuron, 1999

Tailored baseline

- More than 1 Experimental task, each with its own control
- EG: *Are there semantic processing areas in the brain that are modality independent, or do words with the same meaning have separate representations given visual vs. auditory input*
- Visual: Printed words vs. false fonts;
- Auditory: Heard words vs. nonsense speech
- Assumes baseline tasks control for E1 and E2 equally (false fonts are as good as nonsense speech as controls)
- Assumes similar psychometric properties of both experimental and both control tasks: need to test this behaviorally
- Potential solutions: Add an additional common baseline; confirm with direct comparisons

Tailored baseline

- 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 has different levels of selection demand
- Hypothesis: across different tasks, as you increase the selection demands, so does this frontal region increase



Thompson-Schill et al PNAS 1997

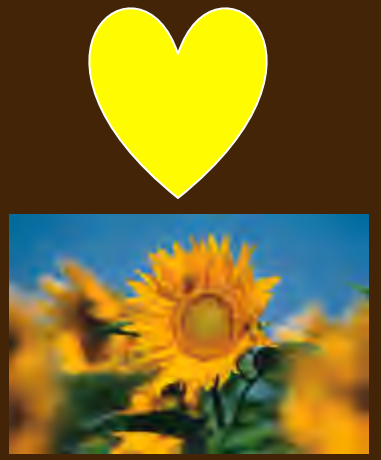
- In such a design you make multiple assumptions
  - Of pure insertion
  - Parametric assumptions: The relationship between task and control is the same across different tasks
  - The differences across hierarchical levels are equivalent across tasks
  - Task assumptions are correct (ie you have correctly 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
-

Factorial design

- A factorial design involves multiple concurrent subtractions
- Allows for testing of interactions between components
- Still requires pure insertion assumption and task decomposition
  - But additivity can be tested for the specific factors that are manipulated

Subtraction vs. Factorial Design
Object recognition vs. “Phonological retrieval”

- A. Colored shape- “yes”
- B. Objects- “yes”
- C. Objects- “daisy”
- D. Colored shape- “heart”

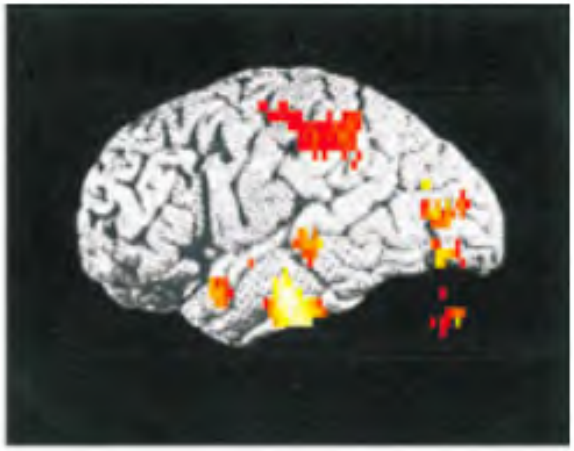


B-A: Activation due to object recognition
C-D: Activation due to object recognition in the context of phonological retrieval
By pure insertion, B-A should equal C-D
i.e., object recognition centers are activated the same regardless of where or not the subject is naming them

From Friston, Price et al 1996

Factorial Analysis

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

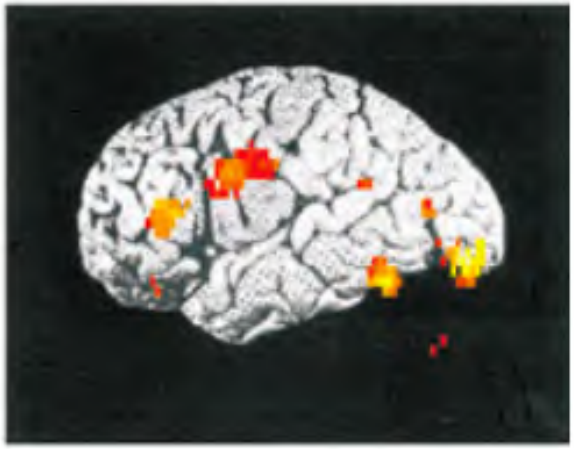


Objects- shapes

(B+C)-(A+D)

Main effect of object rec

B-A

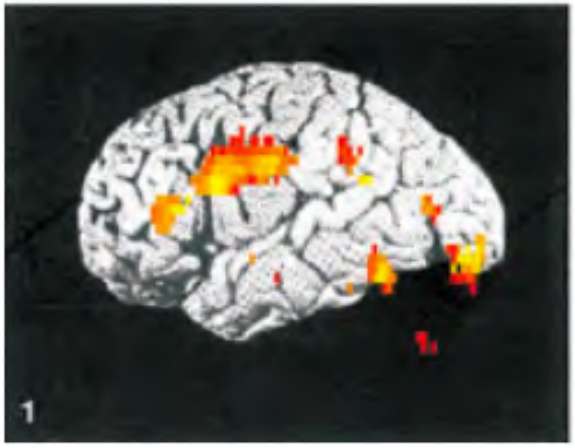


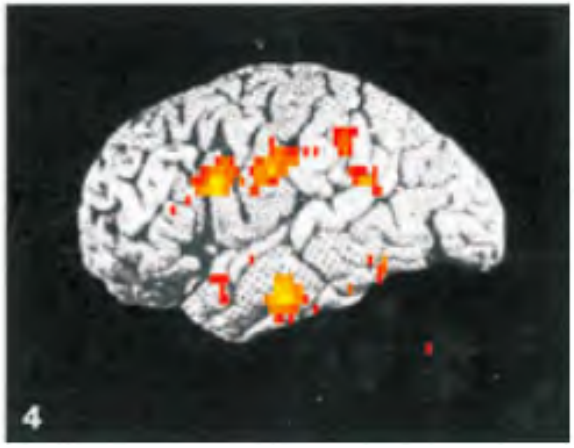
Naming vs “yes”

(D+C)-(A+B)

Main effect of phonol retr.

C-B





interaction

(C-D)-(A-B)

(Obj name-shape name) – (Shape “yes-obj yes)

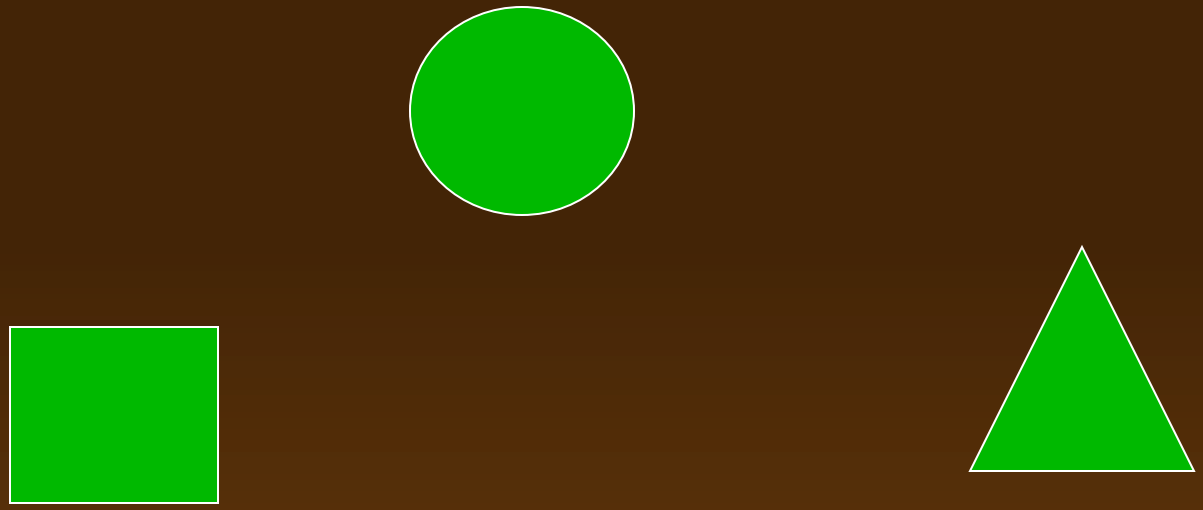
Directed Attention Models

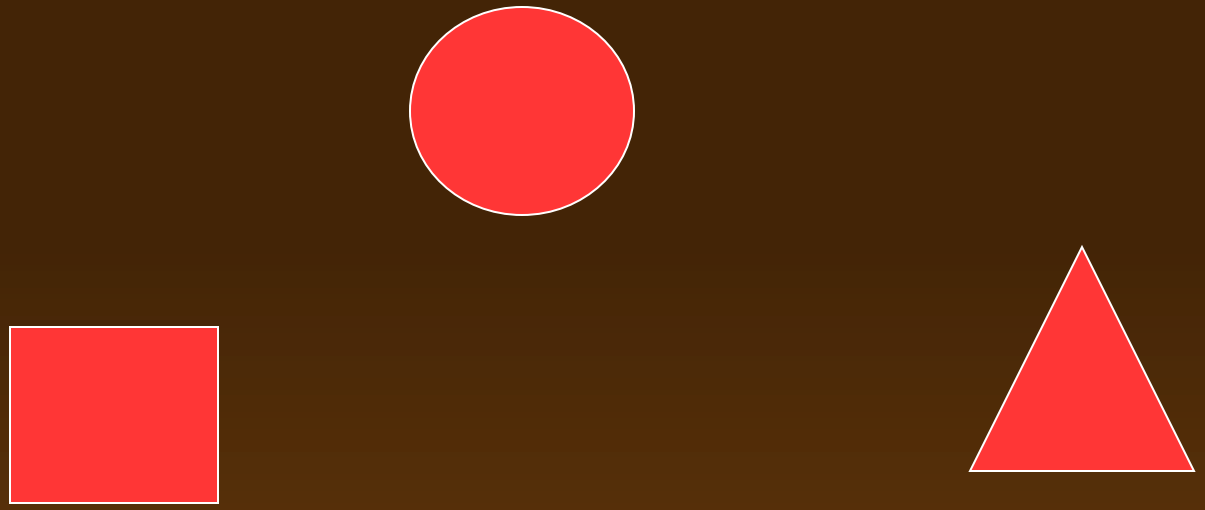
- All stimuli identical in all conditions
- Direct attention towards different features
- Eliminates the need for a control task
- Assumes that the process is modulated by selective attention

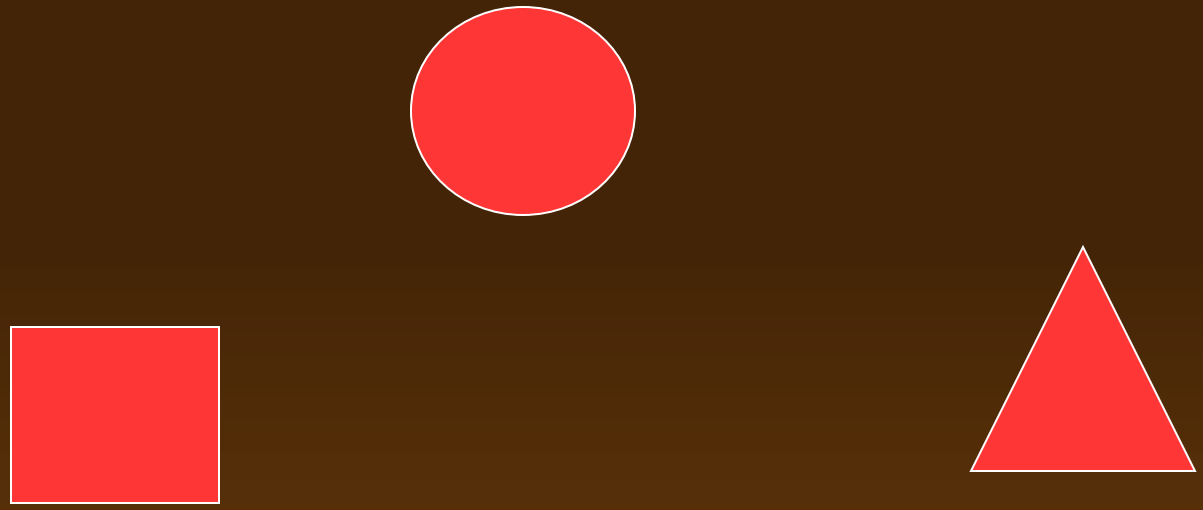
1 **A** B C
2 A **B** C
3 A B **C**

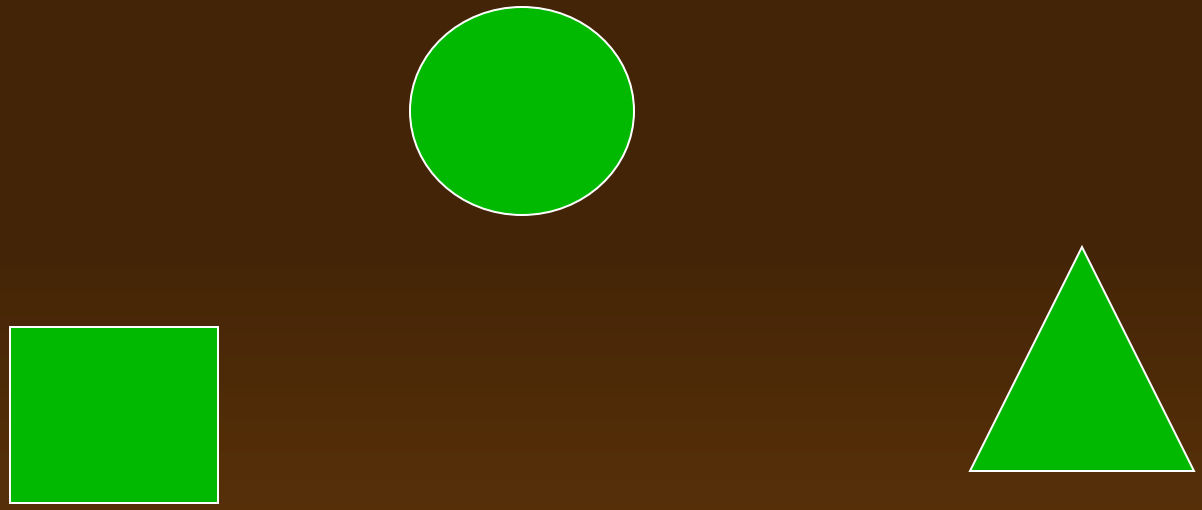
EG Corbetta et al

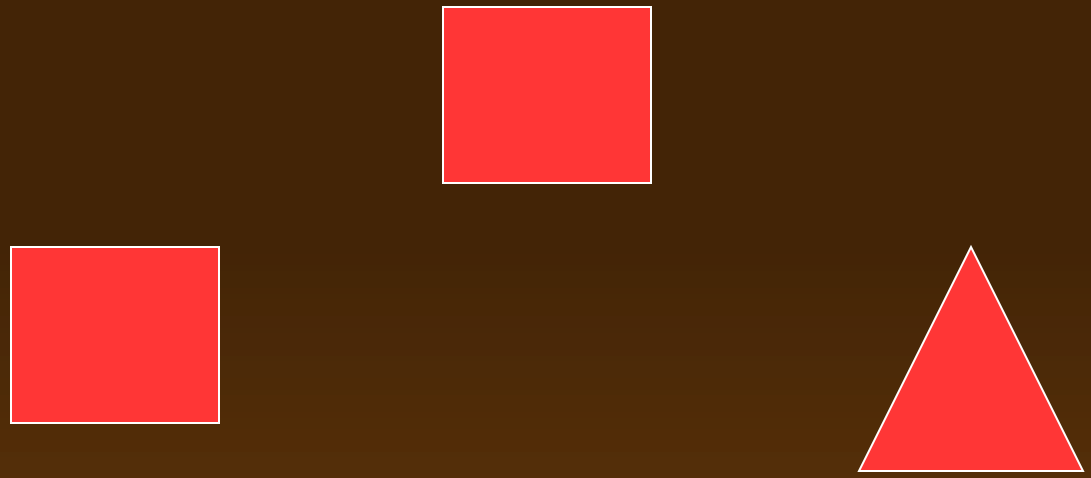
- *Can we identify brain regions that are unique for different aspects of complex visual processing: color, form and motion*
- In every condition, all three variables change; ie stimuli are identical
- Told to respond to a shape, color or movement change in different blocks
- Selectively activates form, color, motion centers











Selective (directed) attention designs

- Implicit or explicit (can have nearly identical conditions, same instructions, but change variables unbeknownst to the subject)
- Assume process is modified by directed attention
- Assume passive processing does not fully capture your variable of interest
- No pure insertion assumptions
- Great choice if you have a process that can be modulated by attention and are worried about contro tasks (multiple experimental tasks)

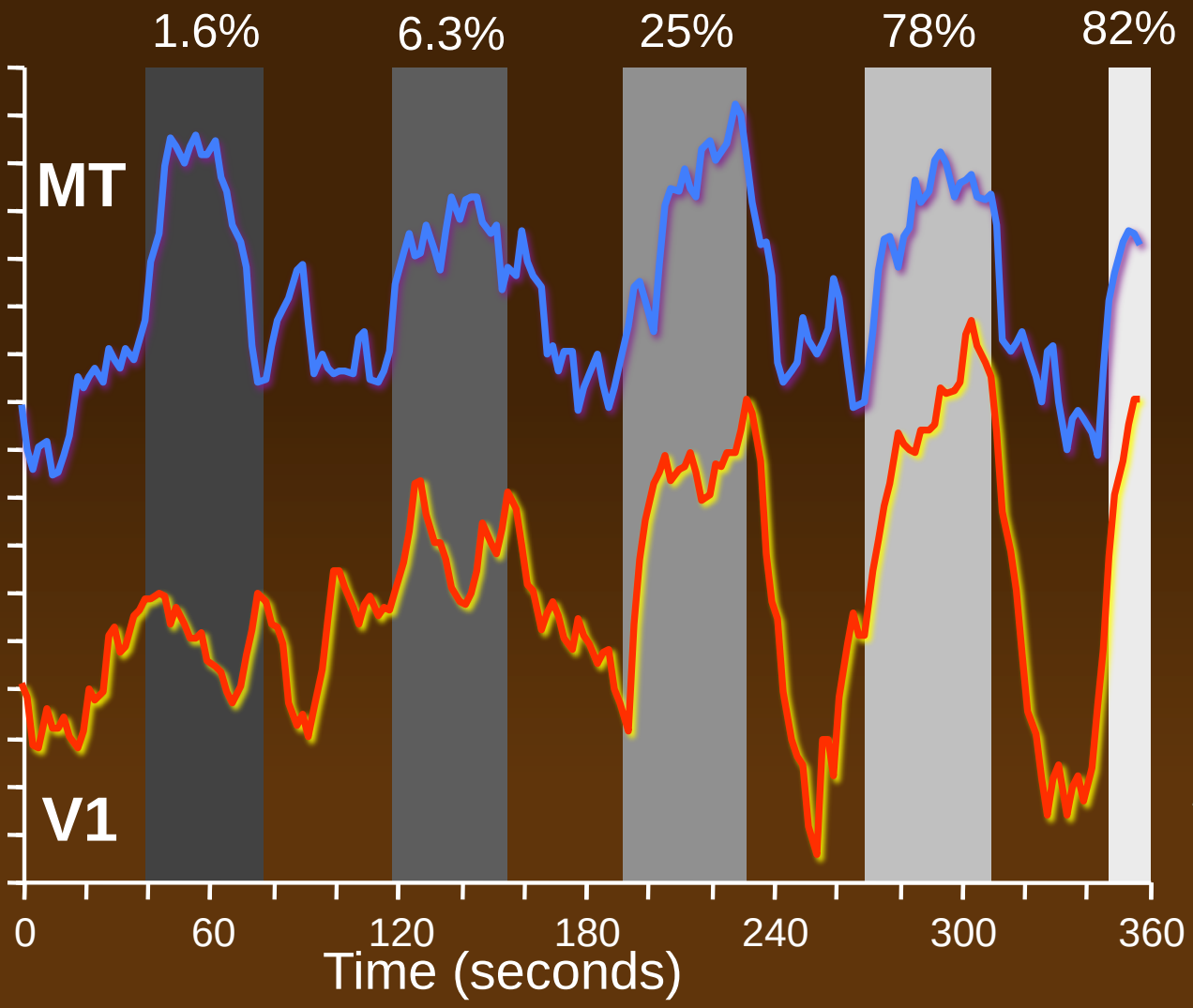
Parametric designs

- Employs continuous variation in a stimulus/task parameter
  - E.g., working memory load, stimulus contrast
- EG: *How does my ROI respond to variations in different task parameters; ie, what computations is this area performing* in
- Inference: Modulation of activity reflects sensitivity to the modulated parameter
- Actually can paramaterize non-linears given a strong hypothesis

A< A < A < A

Contrast vs. Motion responses in V1 vs MT

Parametric variable is contrast;
non-parametric variable (motion vs stationary)

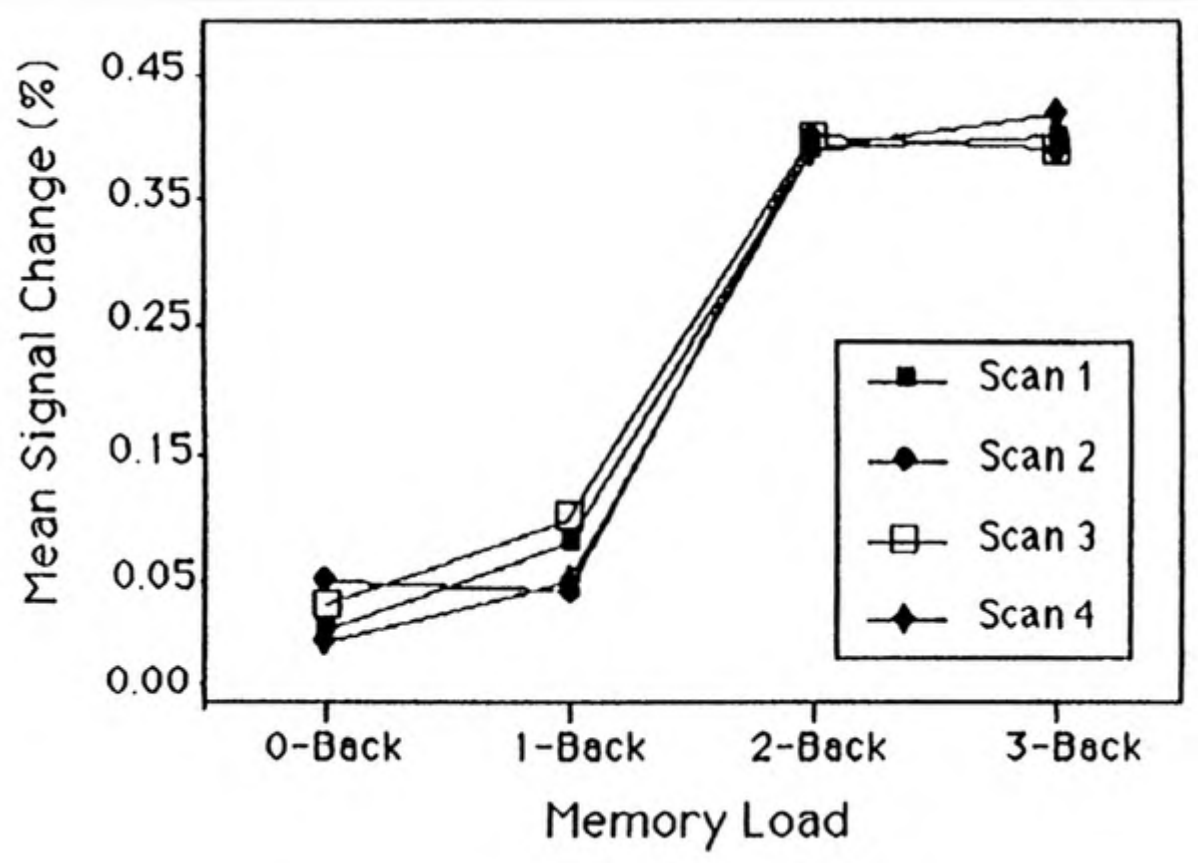


From R. Tootell

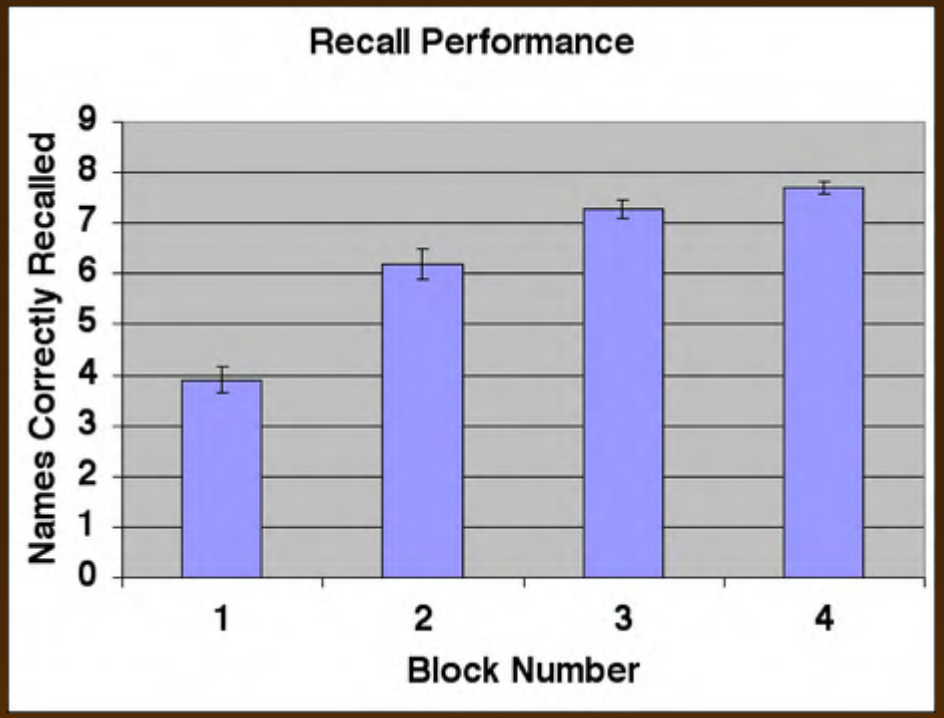
Assumptions of parametric designs

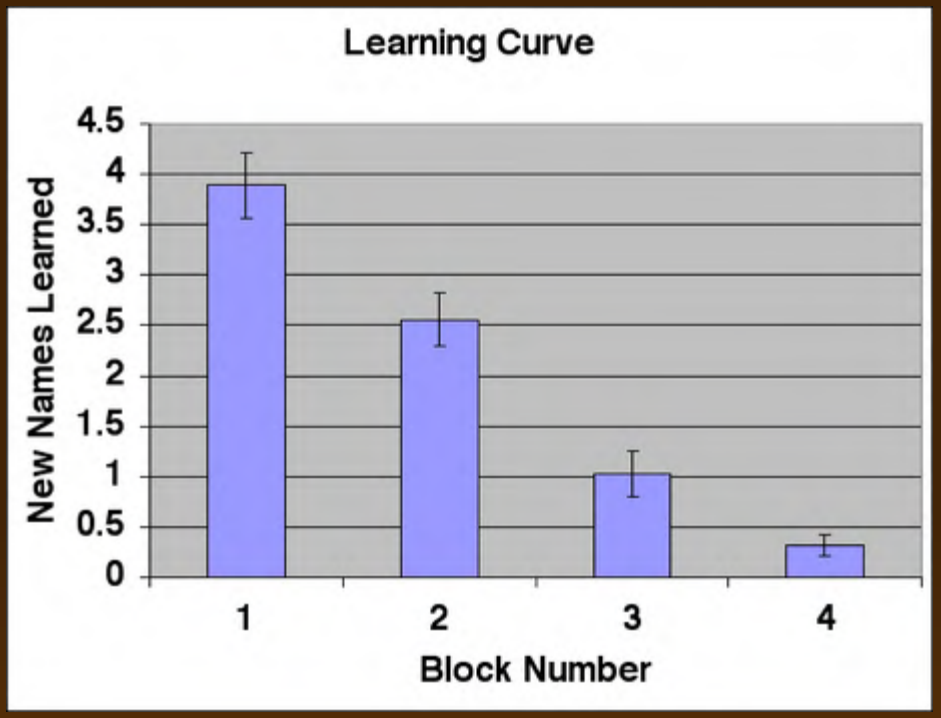
- Pros: you don’t have to design a control condition- no subtraction
- Assumption of pure modulation
  - Each level of the task differs quantitatively in the level of engagement of the process of interest, rather than qualitatively
  - Assumes you can define the magnitude differences across levels (usually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

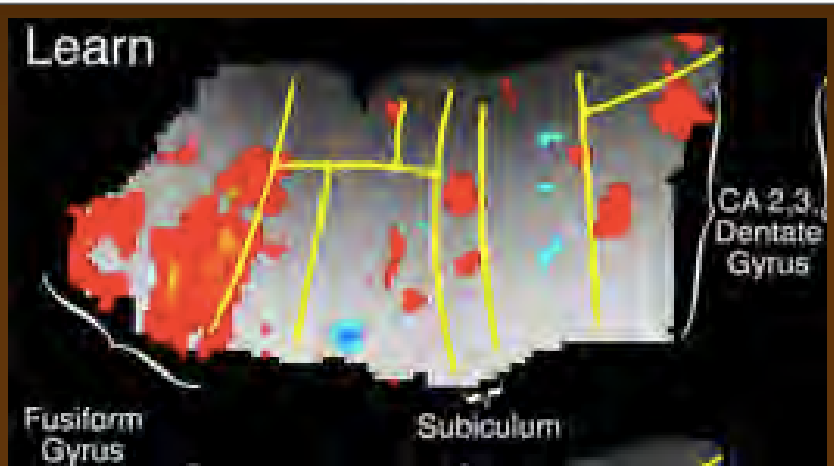
Cohen et al., 1996



Parametric Model based on Memory Performance (Zeineh et al 2003)

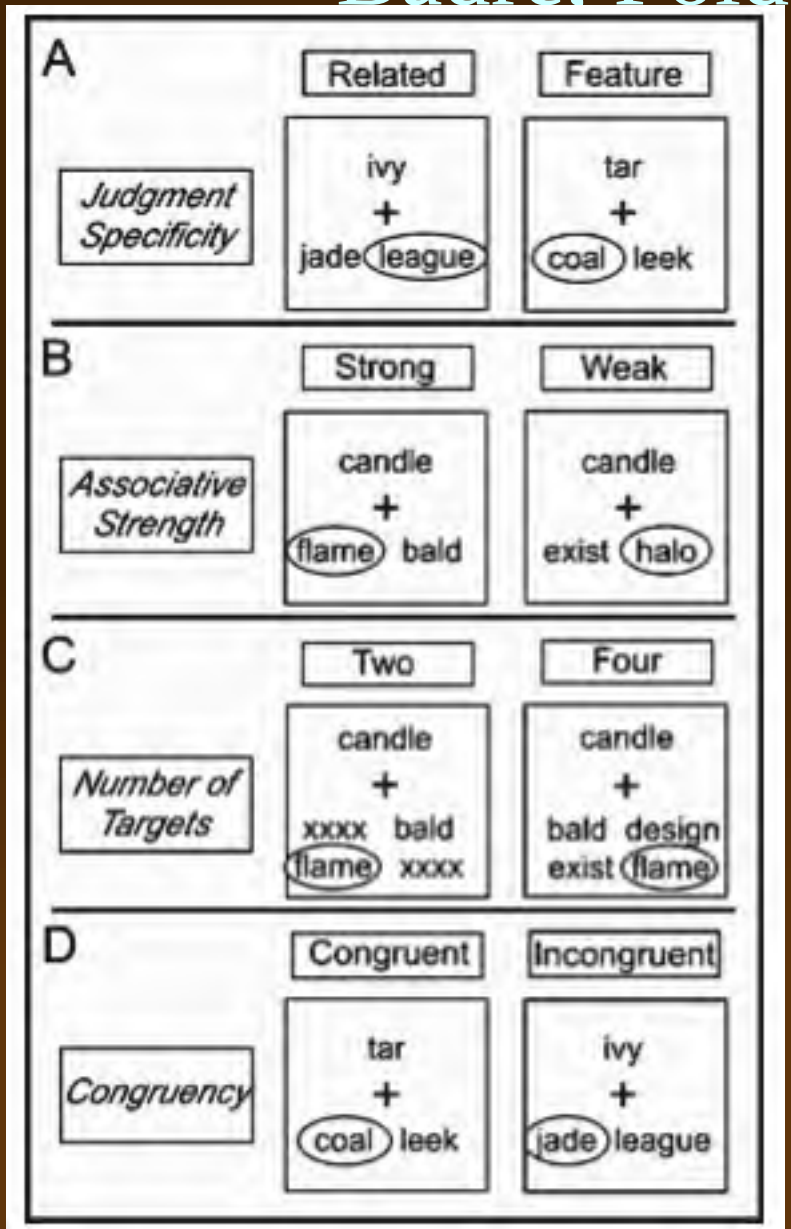


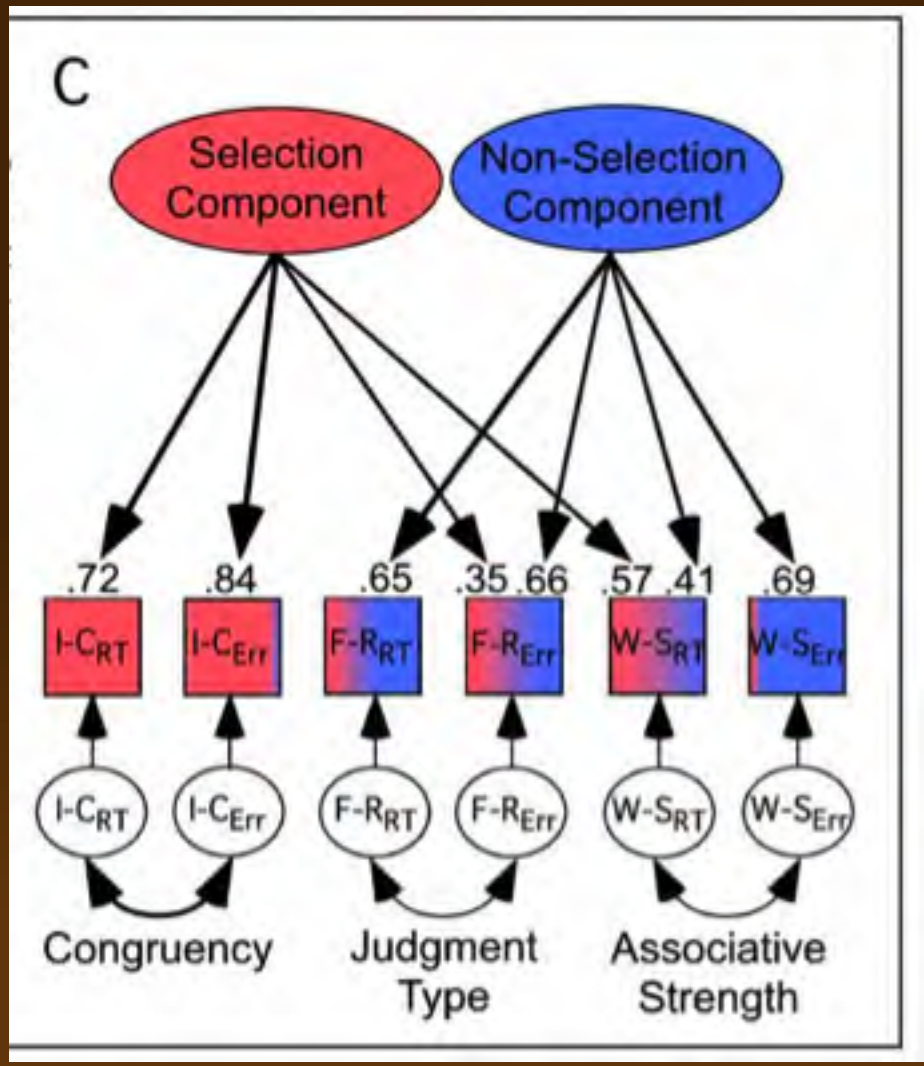




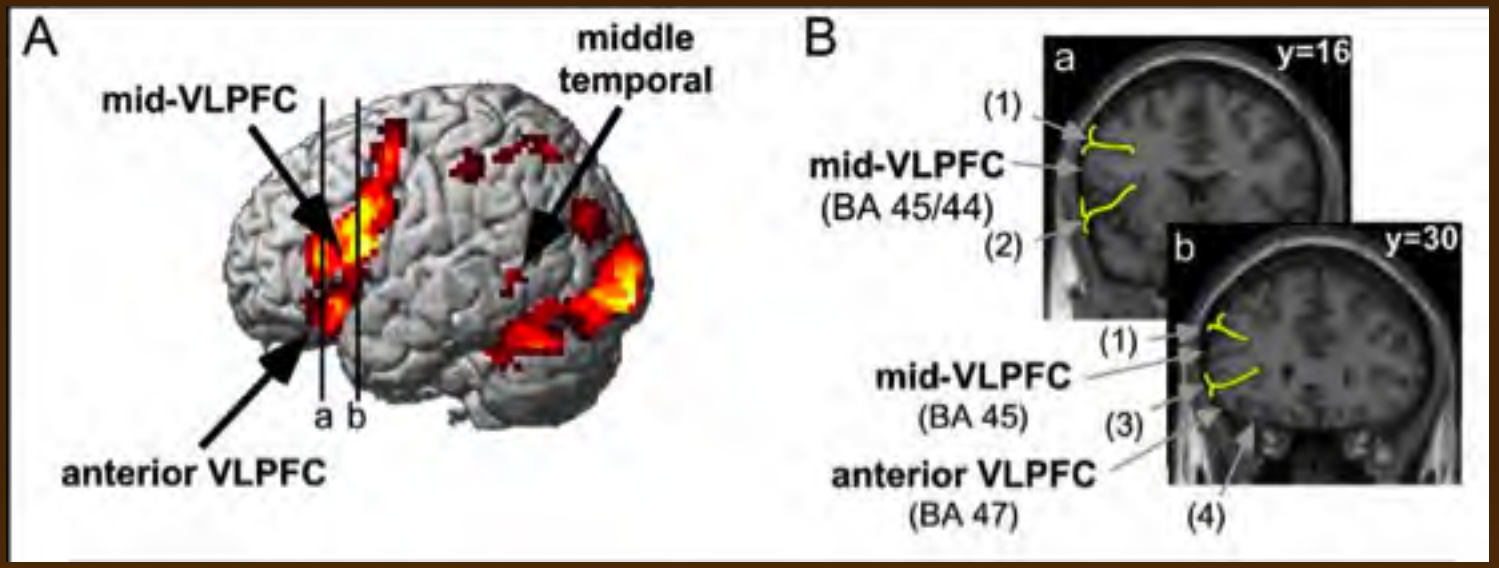
Used as a regression model for learning and retrieval.

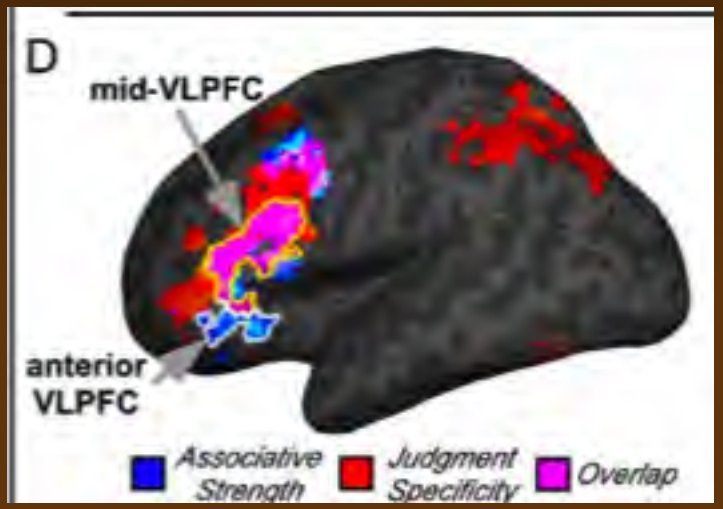
Factor-determined component classification: Badre, Poldrack et al 2005





IFG dissociations





Badre, Poldrack etc 2005

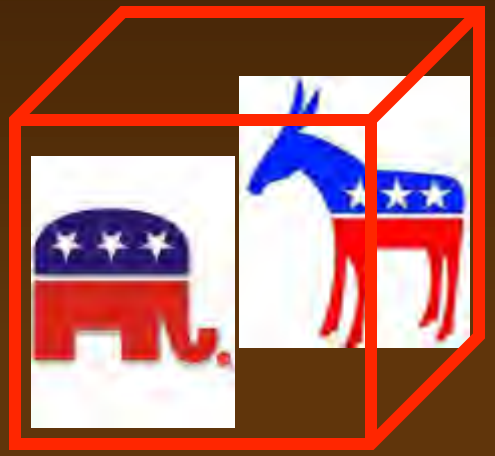
Priming/adaptation designs

- 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

Differentiating what aspects of the stimulus the region (voxel) is computing

EG: Is this region responsive to politicians generally? Or specific to party?

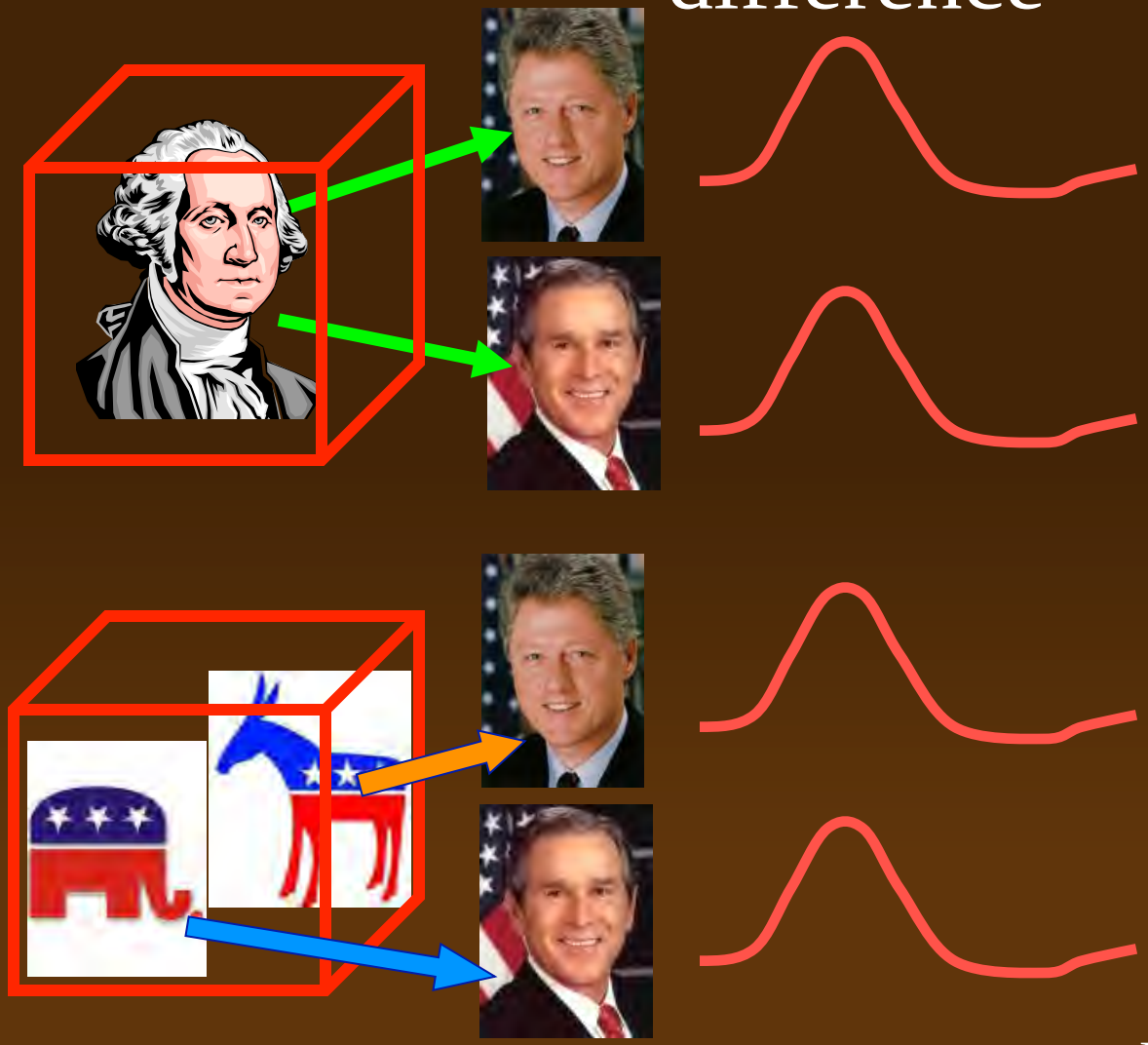
- A voxel containing neurons that respond to all politicians, irrespective of party



- 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



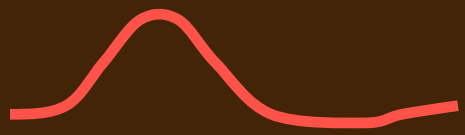
- Different sets of neurons are active within the voxel, but overall fMRI responses are indistinguishable

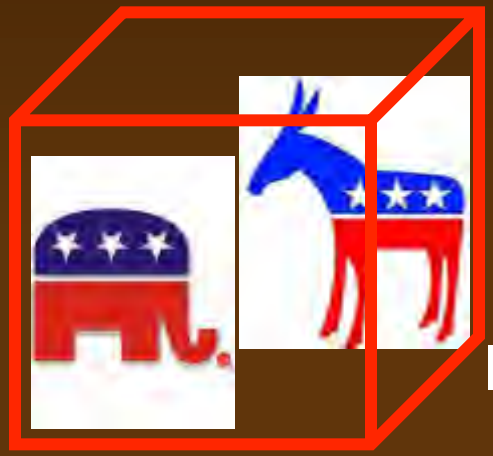
From R. Raizada

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

It’s a politician

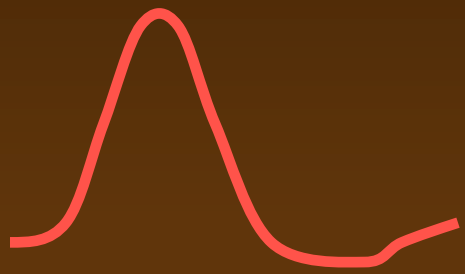
Same neurons, adapting:
It’s a politician again





It’s a Republican

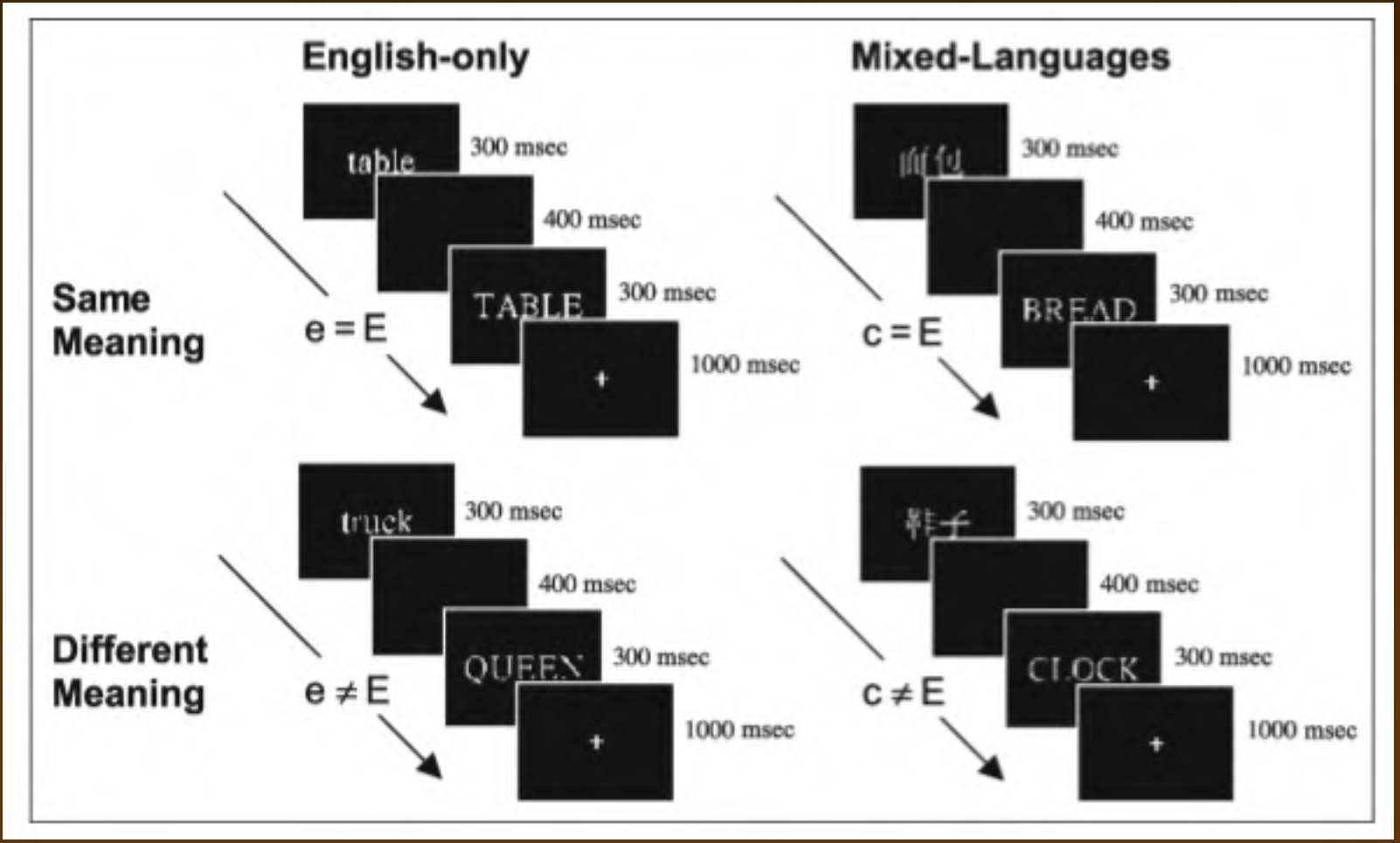
Different, fresh neurons:
It’s a Democrat



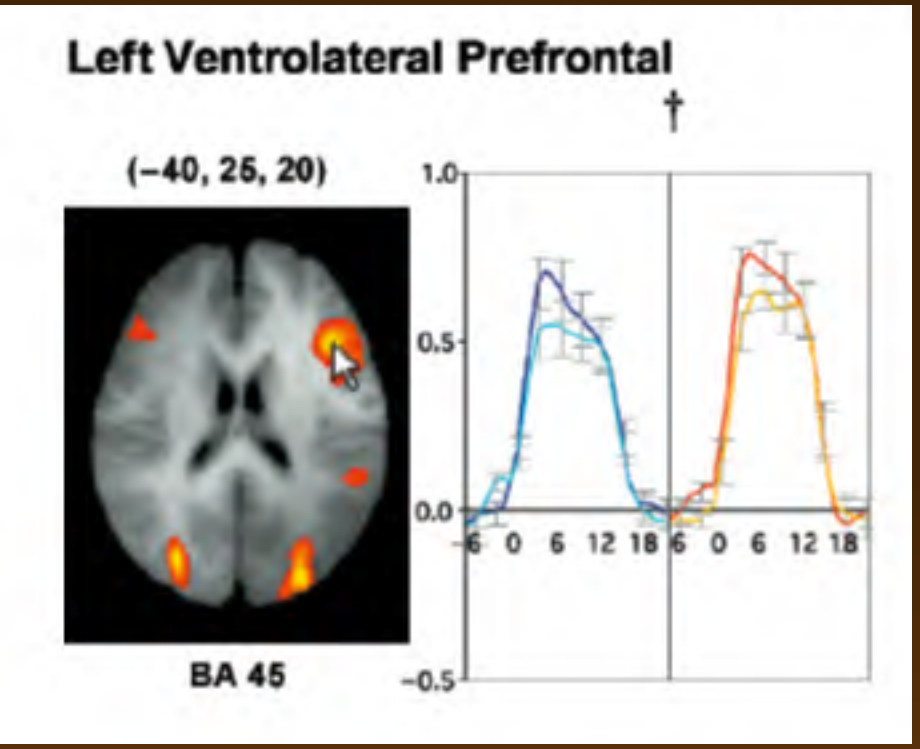
From R. Raizada

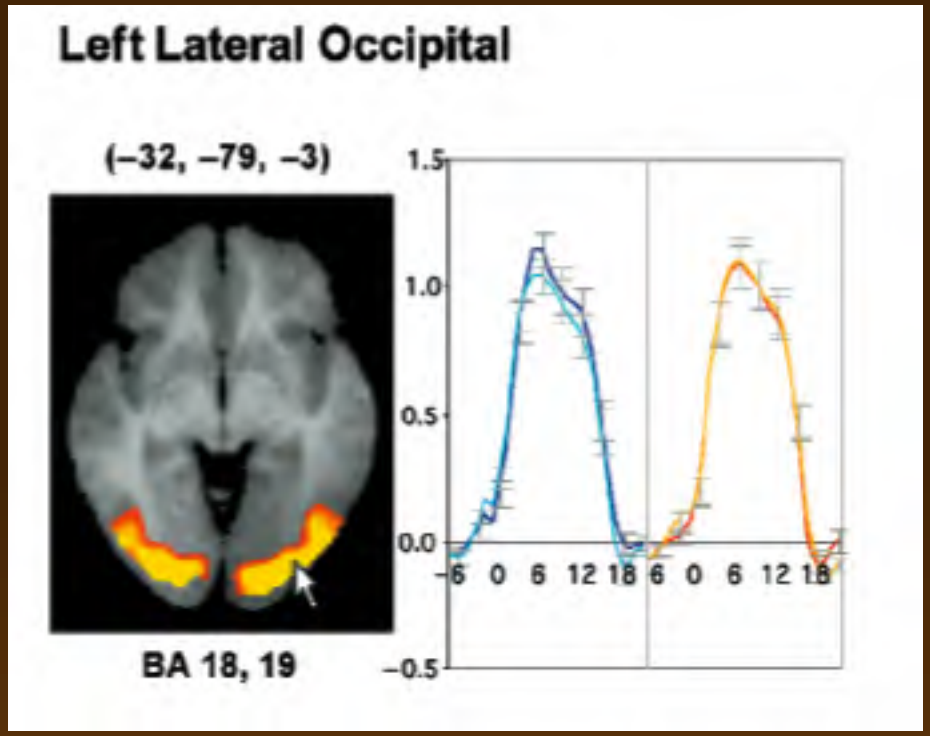
Adaptation in bilingual subjects

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



Chee et al 2003





Main effect for meaning (adaptation) in LIFG, not LOcc

Conjunction analysis (Price & Friston, 1997)

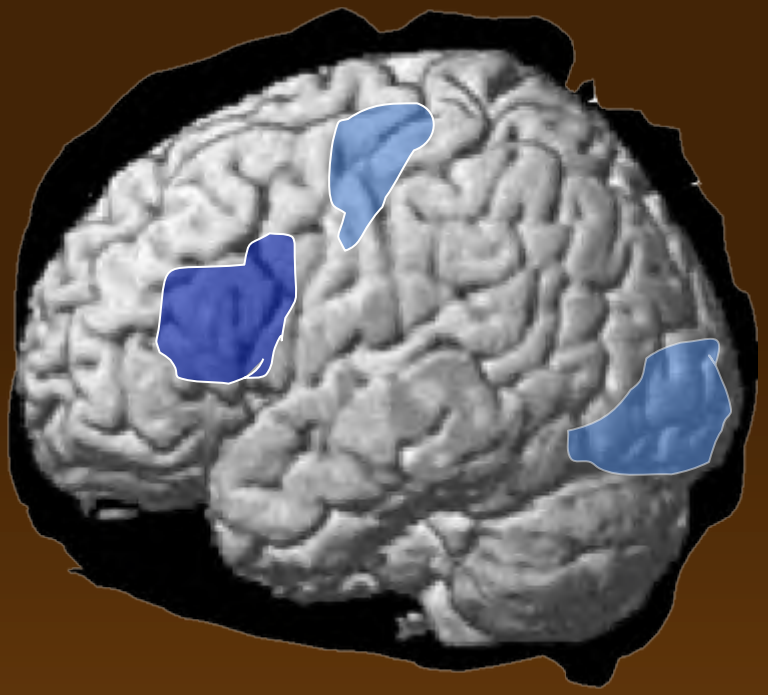
- Perform several parallel subtractions
  - Each of which isolates only the process of interest
- Find regions that show common activation across all of these

Conjunction Analysis

Ex A - Ctl

Ex B - Ctl

Ex C - Ctl

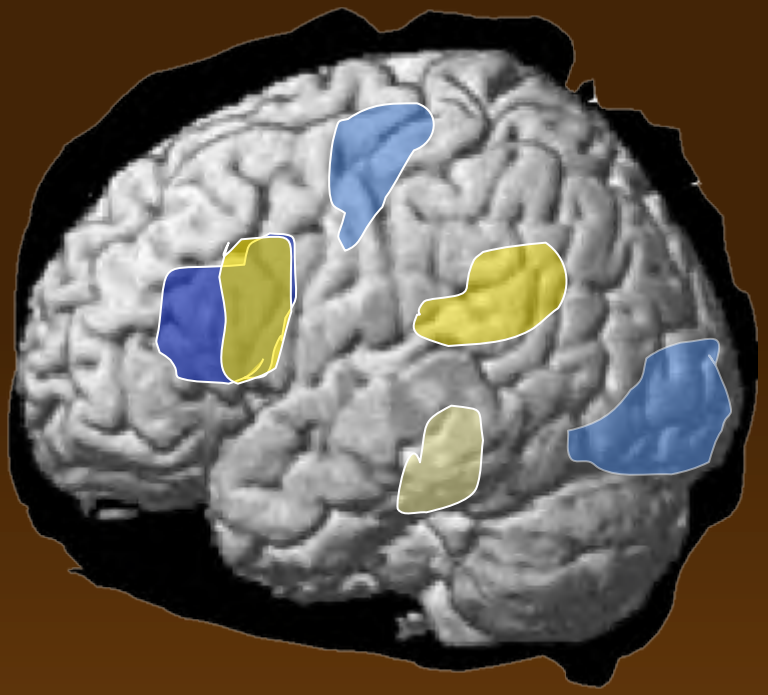


Conjunction Analysis

Ex A - Ctl

Ex B - Ctl

Ex C - Ctl

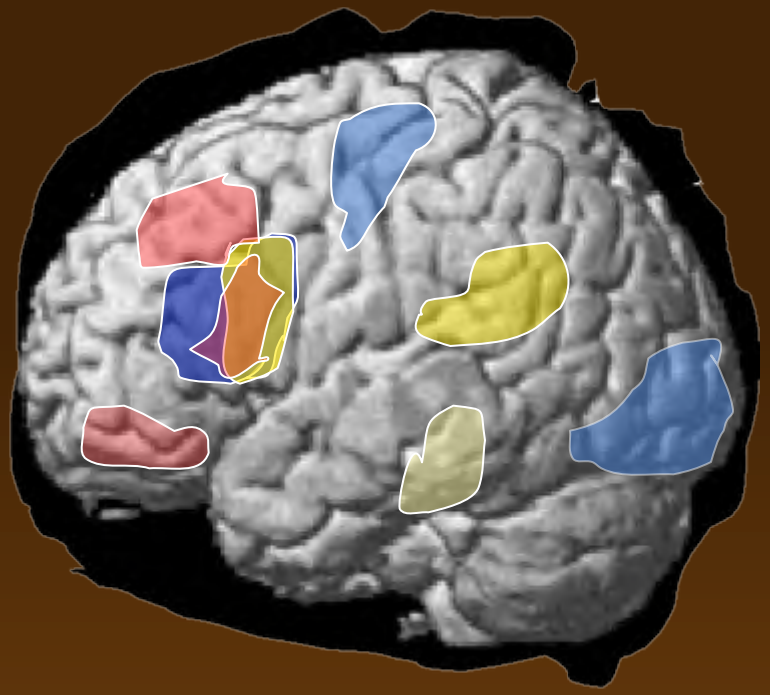


Conjunction Analysis

Ex A - Ctl

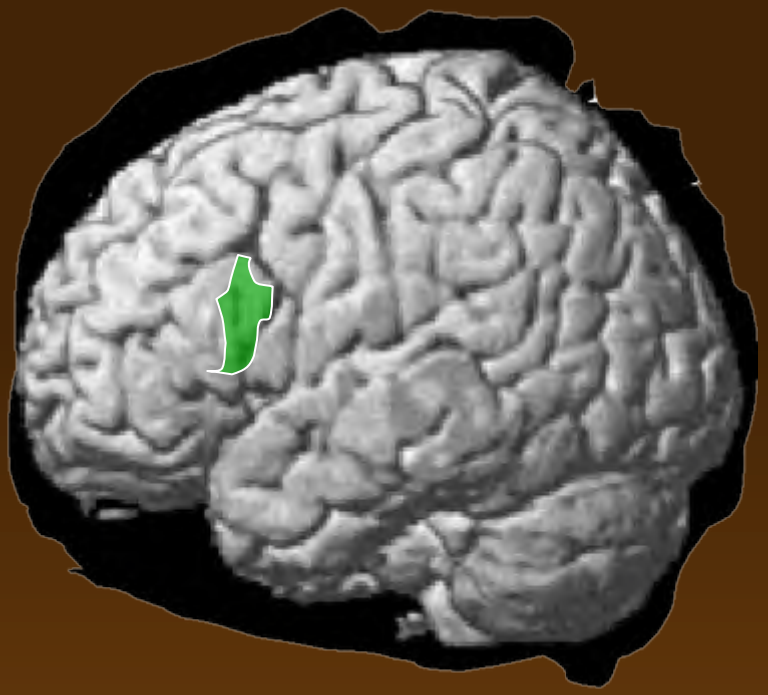
Ex B - Ctl

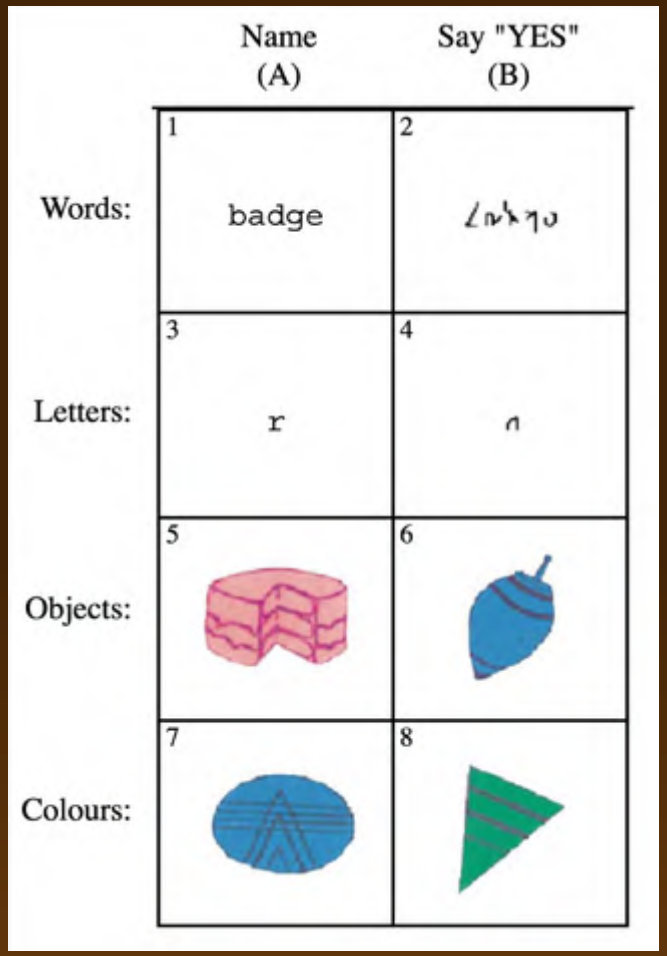
Ex C - Ctl

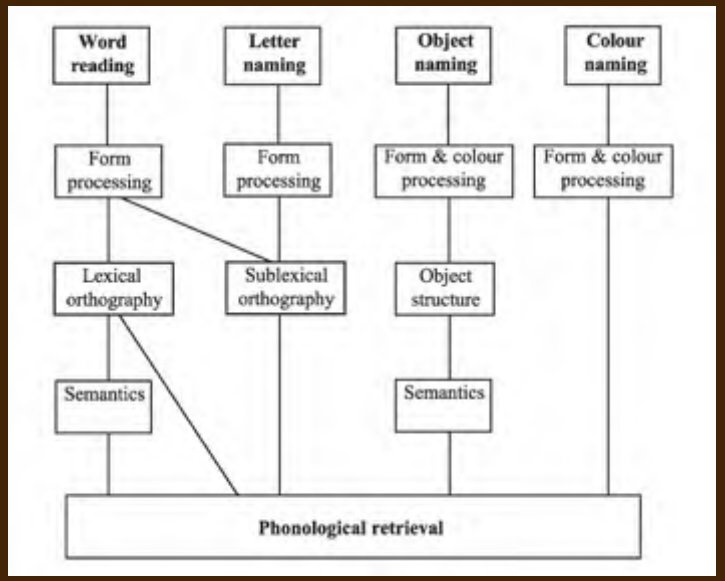


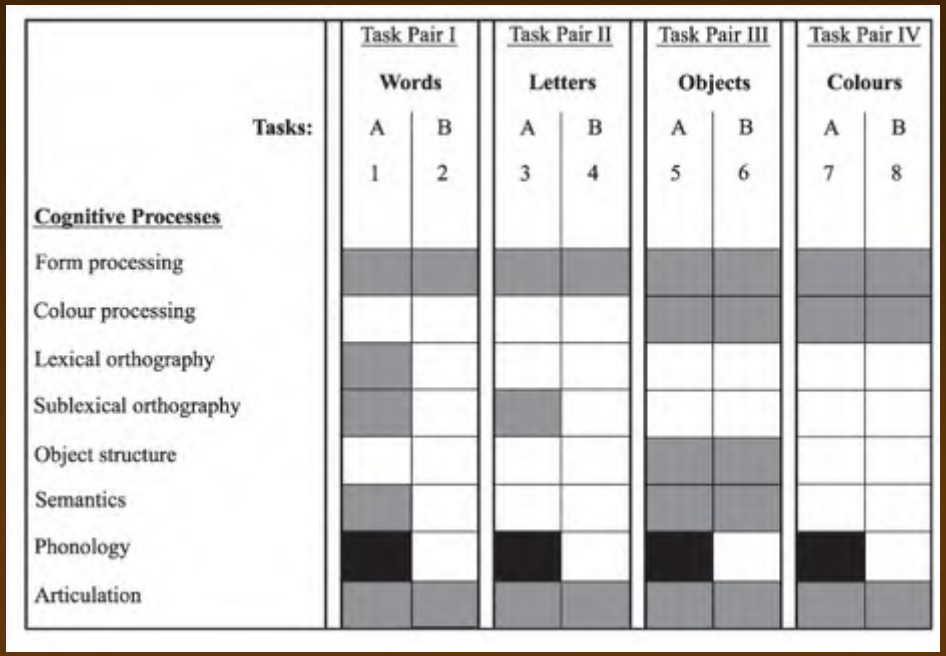
Conjunction Analysis

A AND
B AND
C



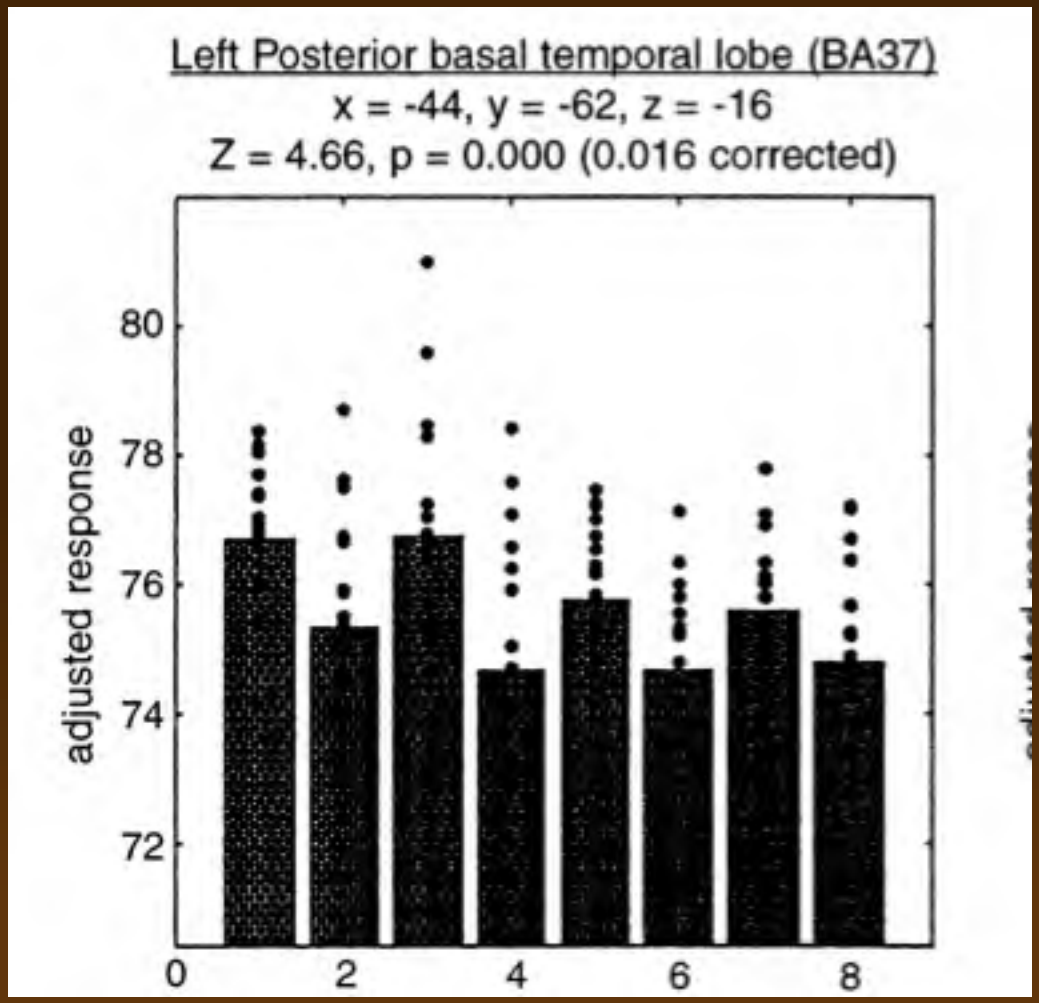






from Price & Friston, 1997

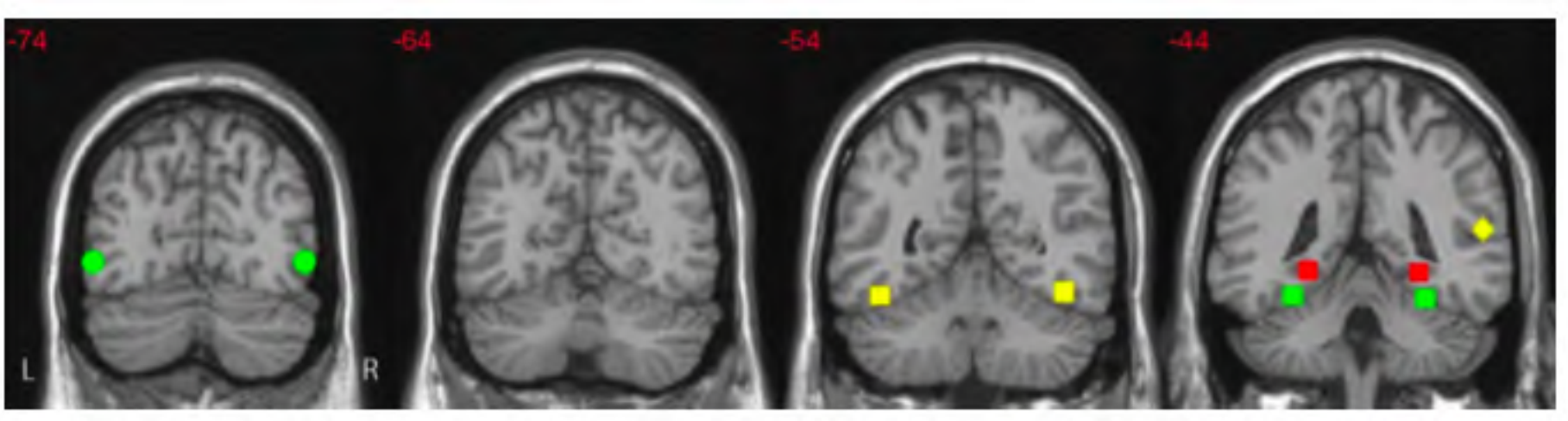
BTLA- all tasks involving accessing phonology

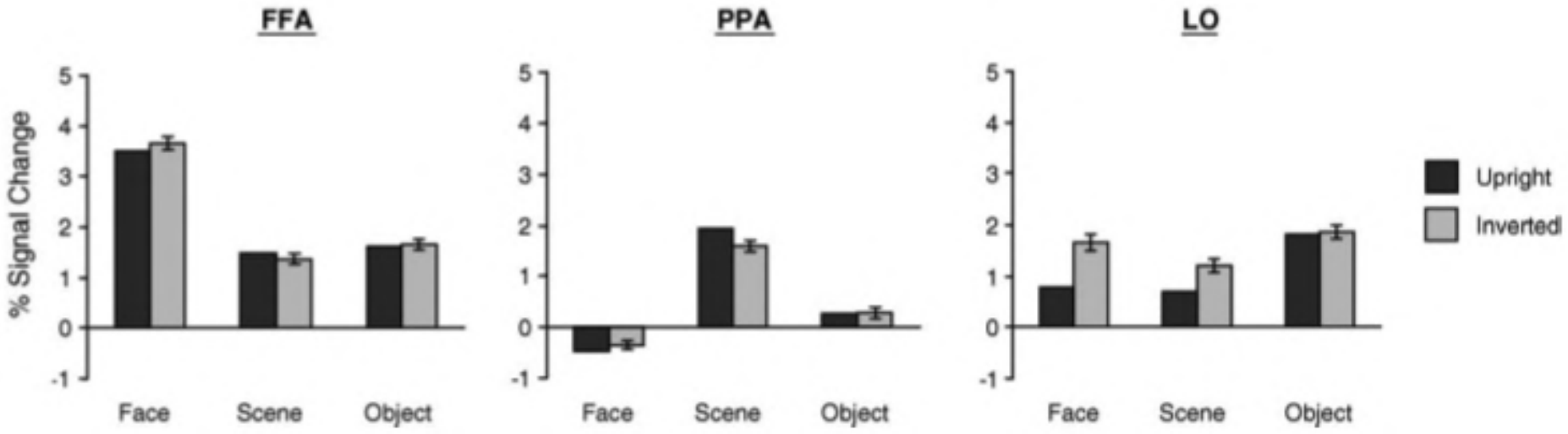


Problems with conjunction analysis (Caplan & Moo, 2003)

- Many assumptions about what processes are involved
- Does not measure magnitude differences
  - Thresholding is therefore a major issue
- 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

Functional Characterization with ROI analysis





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**

Behavioral Testing, Task Difficulty

- If your tasks differ in overall difficulty, you will find greater magnitudes and engagement of additional regions in the more difficult task that may be non-specific and easily misinterpreted as task specific
- If your control tasks differ in “controllness” for multiple Exp conditions, will have misleading magnitude findings
- If the variances among tasks differ, they are not directly comparable- especially in 20group designs

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
- Assumes equal variance of task
- Assumes equal task difficulty
- Assumes equal variance of nuisance measures eg motion
- Always always always do your low level within group comparisons first and interpret them before between group

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
- Look at your data at every step as you go