Experimental Design I

Topics

- What questions can we ask (intelligently) in fMRI
- Basic assumptions in isolating cognitive processes and comparing conditions
- General design strategies
- A few really cool experiments

THE ROYAL SOCIETY

If neuroimaging is the answer, what is the question?

S. M. Kosslyn

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"Attending a poster session at a recent meeting, I was reminded of the old adage 'To the man who has only a hammer, the whole world looks like a nail.' In this case, however, instead of a hammer we had a magnetic resonance imaging (MRI) machine and instead of nails we had a study. Many of the studies summarized in the posters did not seem to be designed to answer questions about the functioning of the brain; neither did they seem to bear on specific questions about the roles of particular brain regions. Rather, they could best be described as 'exploratory'. People were asked to engage in some task while the activity in their brains was monitored, and this activity was then interpreted post hoc."

-- Stephen M. Kosslyn (1999). If neuroimaging is the answer, what is the question? *Phil Trans R Soc Lond B*, 354, 1283-1294.

Some reasonable questions

- Charting the territory: what does a particular brain region do? How does it compute the information presented? how specific is this region for certain types of information or certain processes?
- Understanding the process: Can we learn more about a cognitive process by imaging the brain in action (than by doing a reaction time or performance test instead, eg)
- Relating to external variables: how do patterns of brain activation relate to differences in subject attributes like genetics, skills (not

Some not great questions or conclusions

- What brain areas light up during my task
  - Since these areas light up during my task, they must be essential for that task
  - Ditto for a presumed cognitive process
- How do 2 groups differ on this task (where that task defines the group difference)
  - Eg reading

We want to design experiments that <u>need</u> brain imaging to answer our questions; otherwise, this is a very expensive neuropsychological test

Conceptual and methodological aspects of experimental design

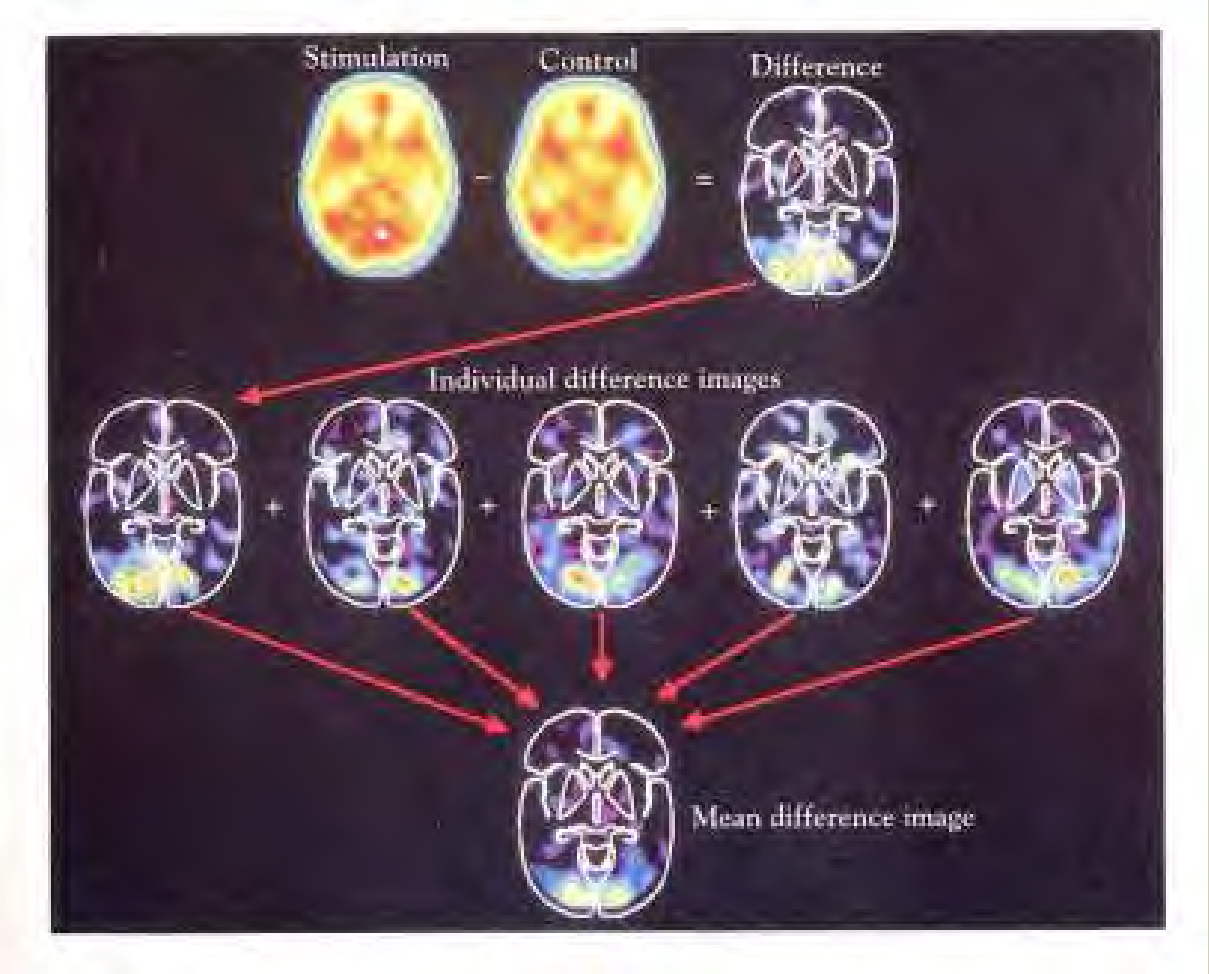
- There are two aspects of fMRI design that are important to distinguish
- Conceptual design
  - What neuroscience question are you trying to answer?
  - How do we design tasks and control conditions to properly measure the processes of interest?
  - The issues here are very similar to those in cognitive 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.

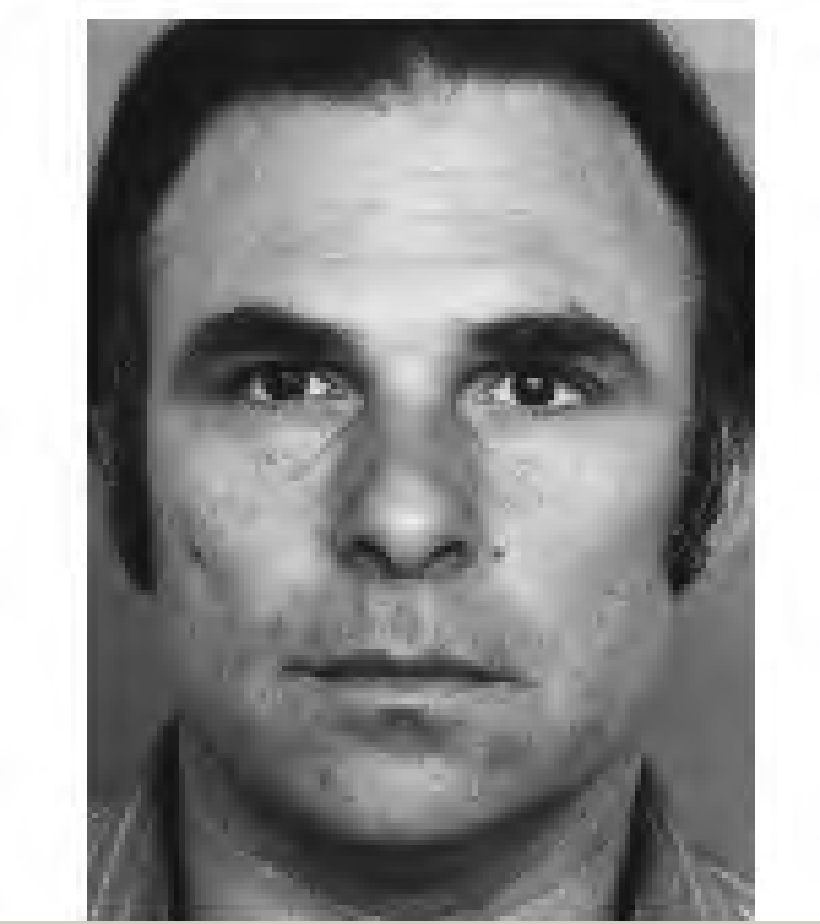
The subtraction method

- Acquire data under two conditions
  - These conditions putatively differ only in the cognitive process of interest
- Compare brain images acquired during those conditions
- Task – control = the process of interest
- “Pure Insertion Hypothesis”



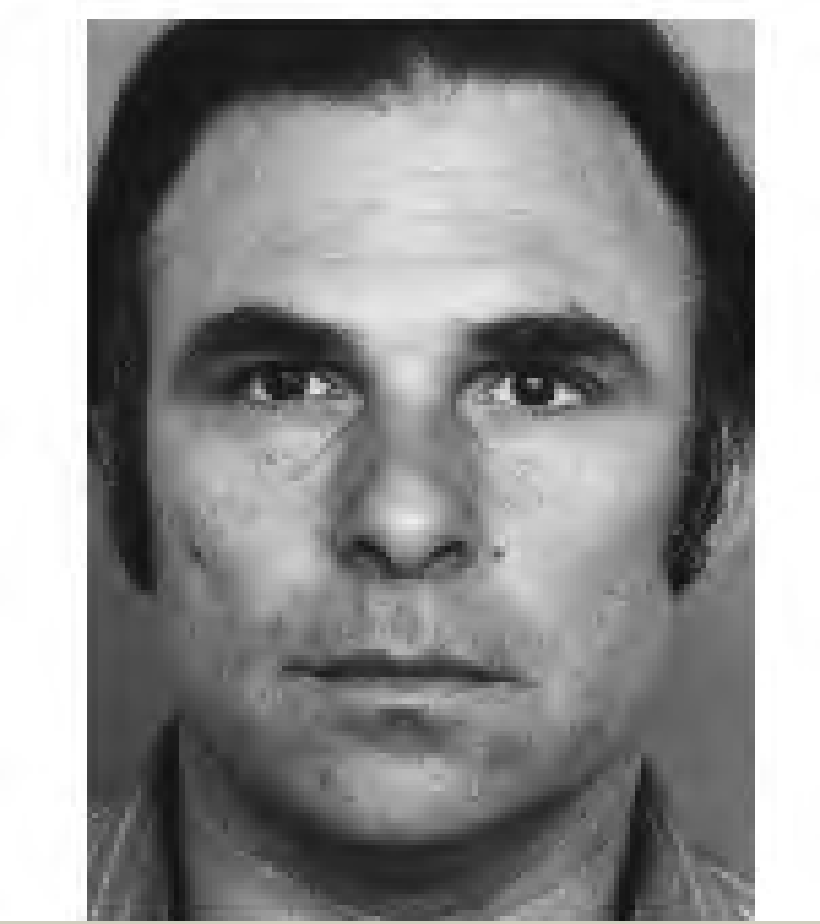
Petersen et al., 1988

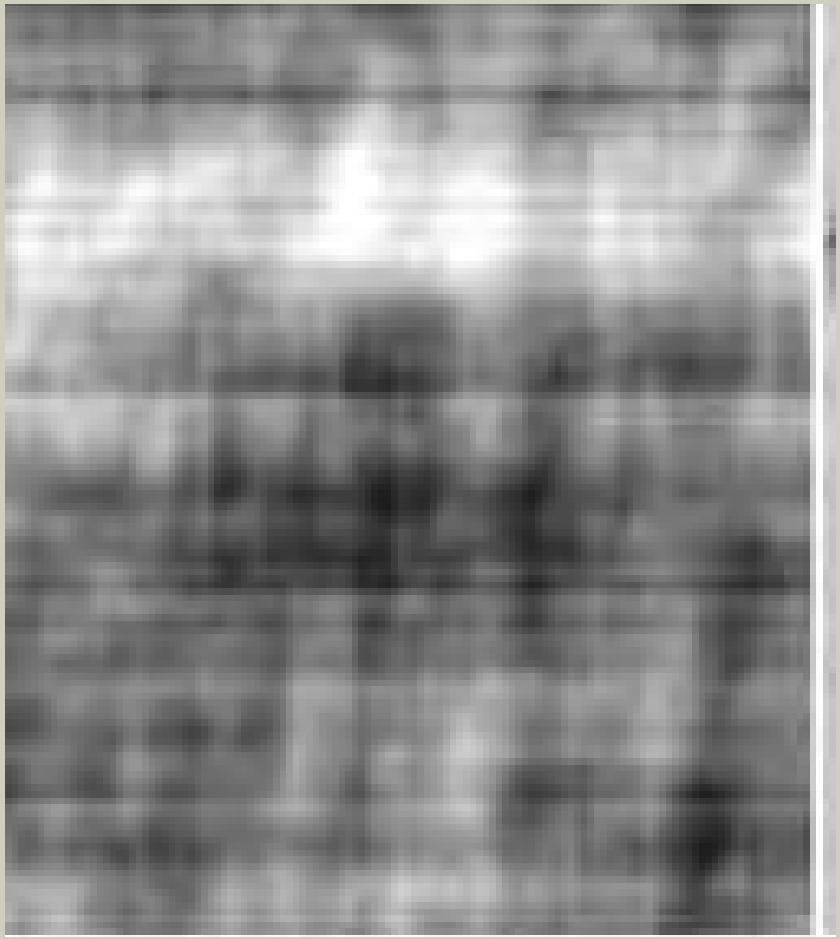
Eg face processing



Face – scrambled face = face area

Eg face processing





Face – scrambled face = face area

Controlled for visual stimulation; luminance, contrast, average spatial frequency etc

The task analysis assumption

- Subtraction assumes that your task analysis is correct: you have defined all of the processes engaged in this task
- Assumes that you controlled for everything except the process of interest
- In this example, we controlled for all visual aspects; are we left with only face processing? What else might differ between task and control?

The task analysis assumption

- What else might differ between task and control?
  - Familiarity/novelty
  - Salience of stimuli
  - Attention to stimulation
  - Interest in stimulus
  - Emotional reactions
  - Language- naming the kind of stimulus
  - Memory- he looks like my uncle John
  - Cognitive: he looks like an ax murderer

Do the best you can, but question your assumptions

Pure insertion assumptions

- In hierarchical models: my process of interest remains constant (in the brain) regardless of other processes
  - EG: Reading silently vs. reading aloud

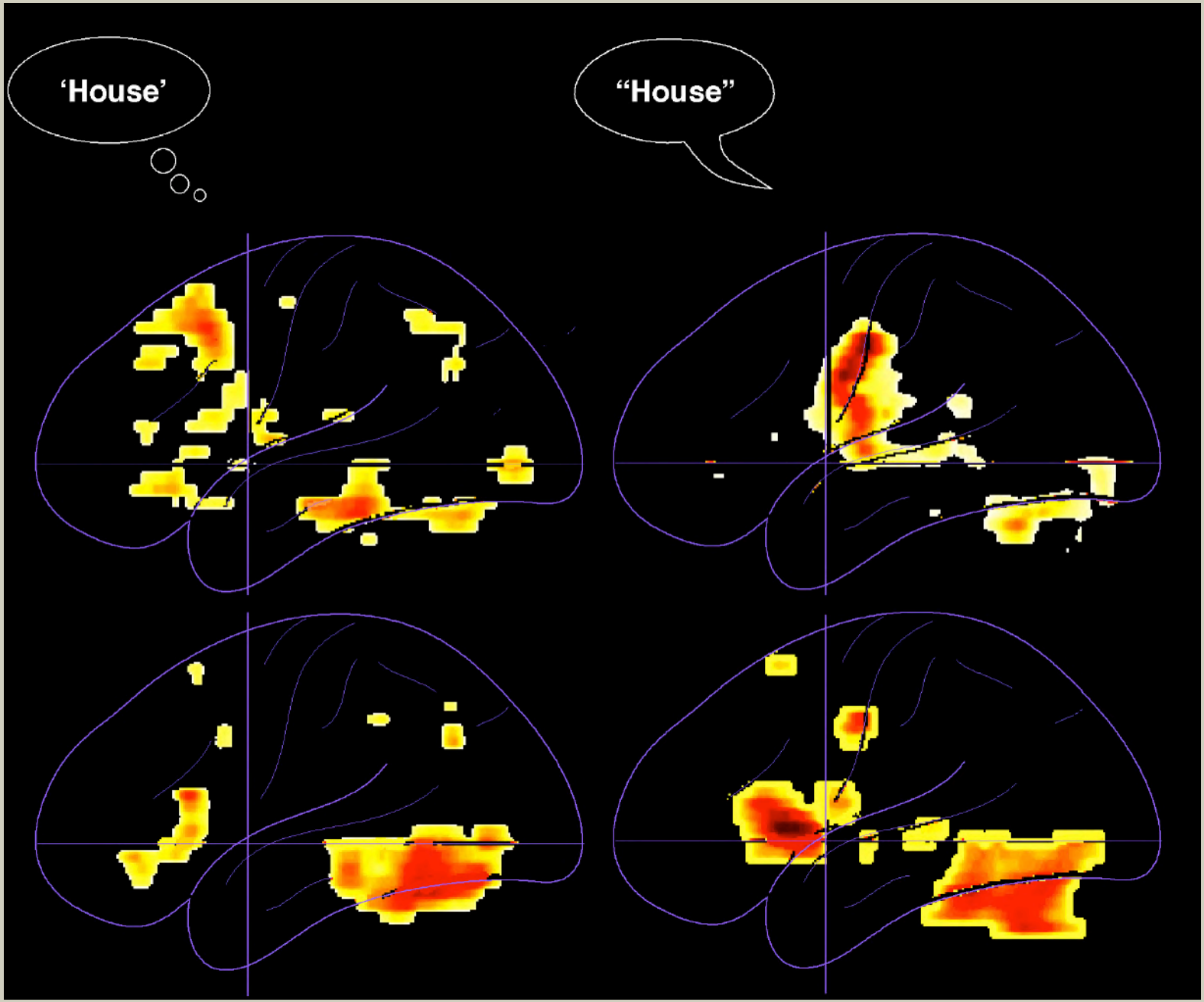
1) False fonts (control)
2) Silent reading (word form areas; semantic areas)
3) Reading aloud (word form areas, semantic areas, motor areas

Assumption: word form and semantic area activations are the same in reading silently vs. reading aloud

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

Read
"**HOUSE**"

Name



Common confounds with control tasks

- Attention required, or task difficulty, is greater in activation compared to control task
  - Pretesting task with RT, performance can help
- Assuming you know the processes involved in task and control
- Over-controlling in the control task
  - You can subtract out processes of interest if they are engaged automatically
  - Eg: nonsense speech is not a great control for real speech. Why? We try to interpret speech sounds. Nonsense speech is complex and novel. We may increase attention to speech areas in this task

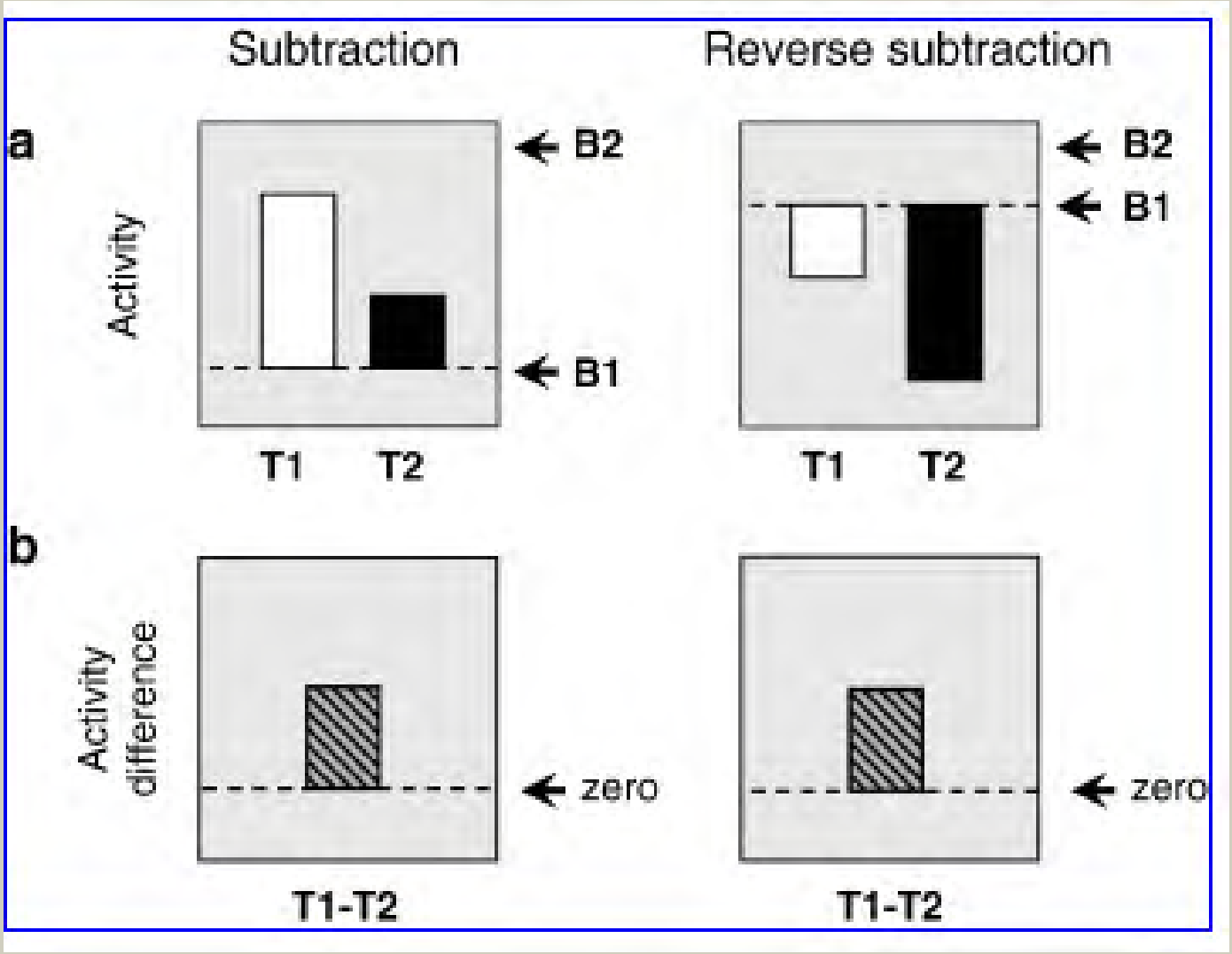
More confounds

- Novelty: item or task repetition usually results in decreased activation the second time around; always control for task/stimulus order
  - Event related designs: randomize and optimize
  - Blocked or mixed designs, counterbalance
- Calculate the number of variables and conditions to get number of different orders you require
- Complete counterbalance: when responses to one condition may affect what follows- order interactions (eg, mood induction)

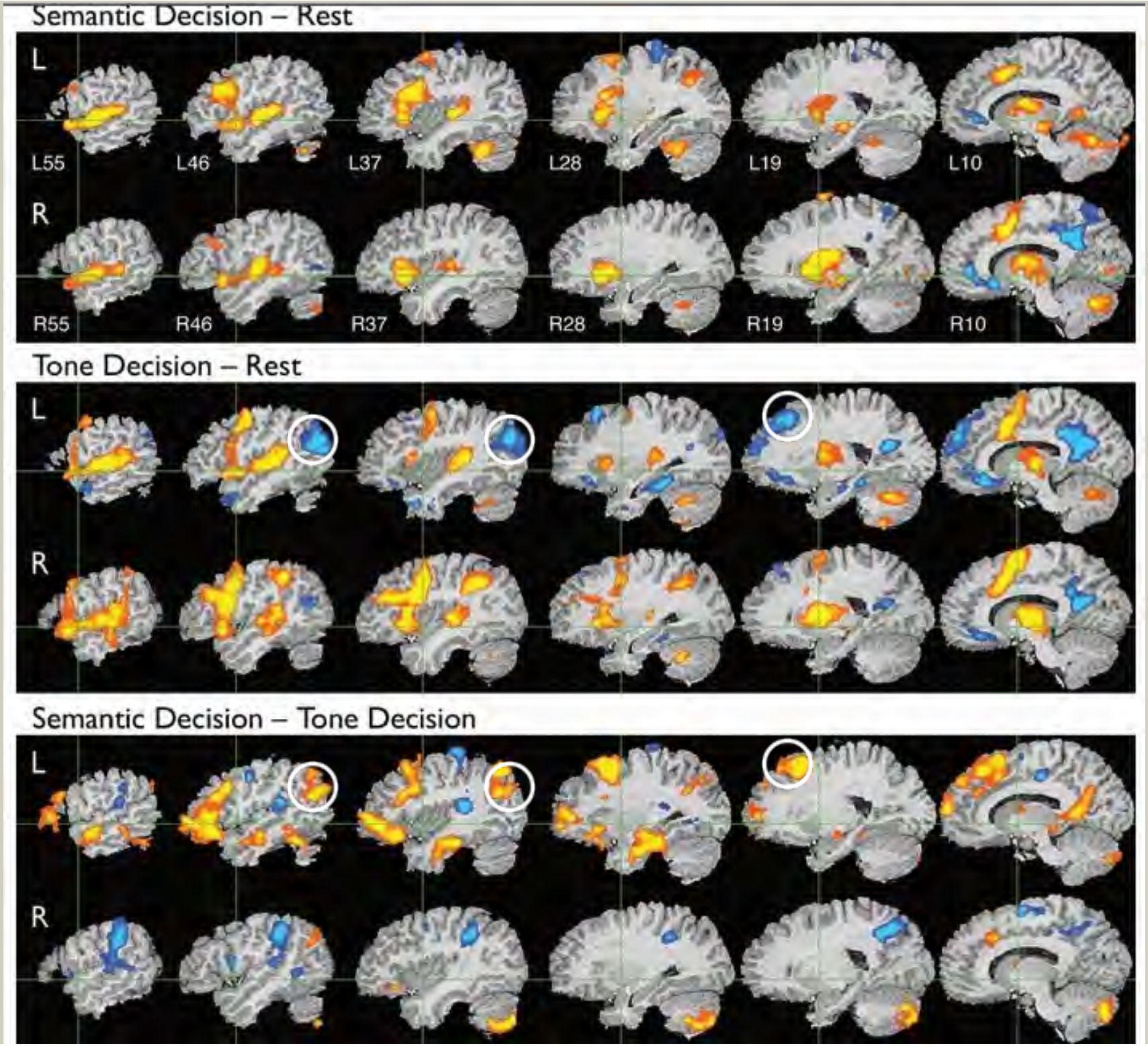
-In 3 conditions, 3! orders: 123, 132, 213, 231, 312, 321

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

General experimental designs

- The problems in finding the “right” control conditions and accurately interpreting your data are independent of timing, ie, block vs. event related.
- Beware the “un-modeled” parameters that go into your baseline for comparison

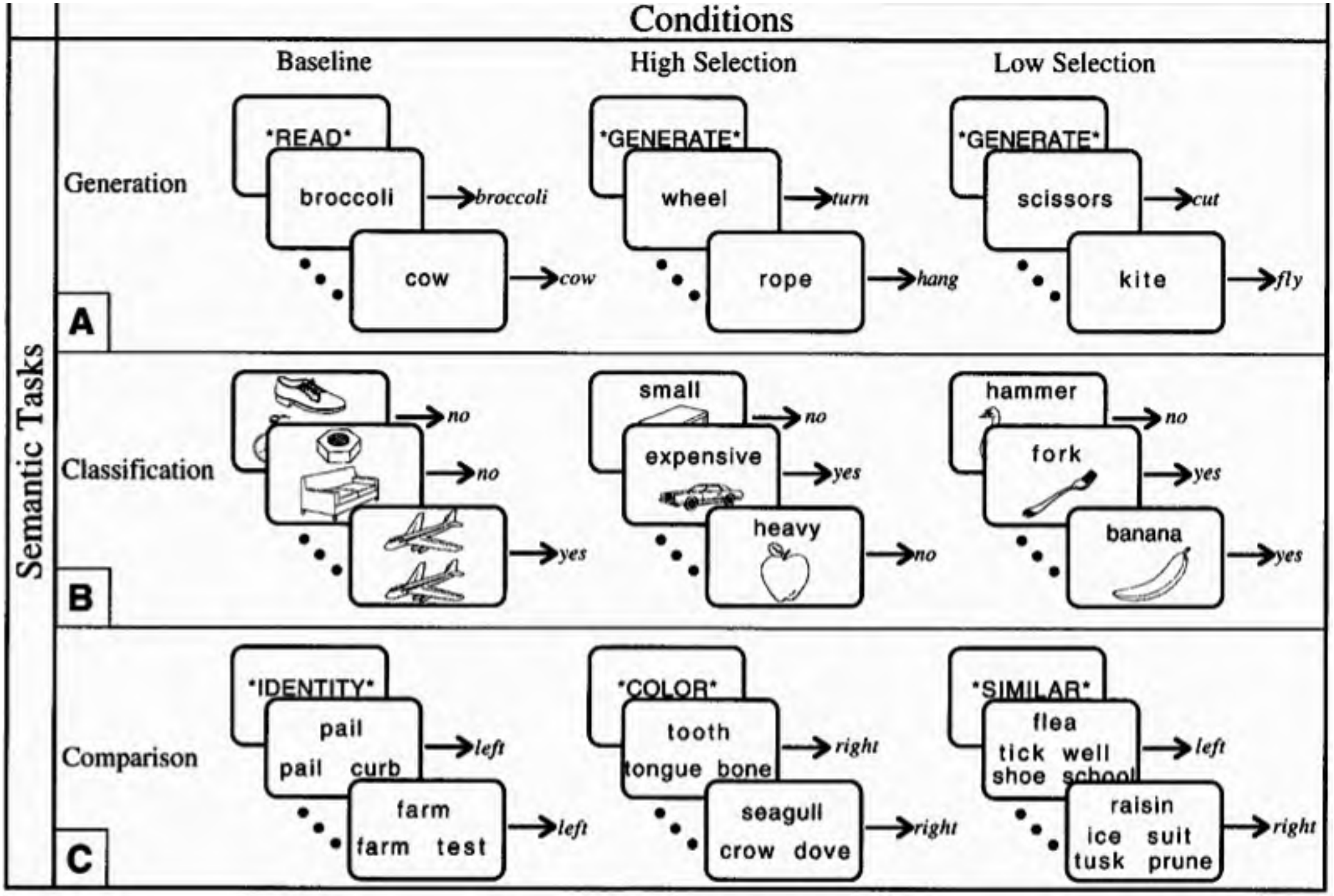
Common subtraction paradigms

- A > B: simple subtraction (don’t forget “deactivations”. And don’t call them deactivations).
- A>B, B<A: Parallel Comparison. Show task-specific (but not shared) regions.
- Assume comparable difficulty/effort/attention, etc.
- Hierarchical designs: A>B>C
  - Requires a strong pure insertion hypothesis
  - The more levels of hierarchy, the more assumptions you make. Oops.
  - Try multiple control conditions to help sort out

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



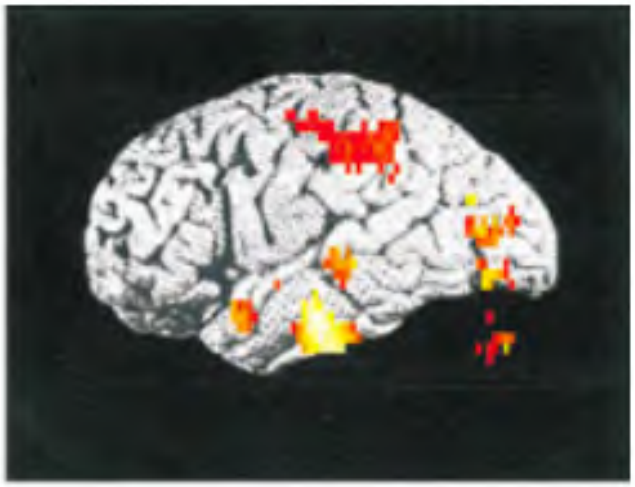
Thompson-Schill et al PNAS 1997

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

Factorial Analysis

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

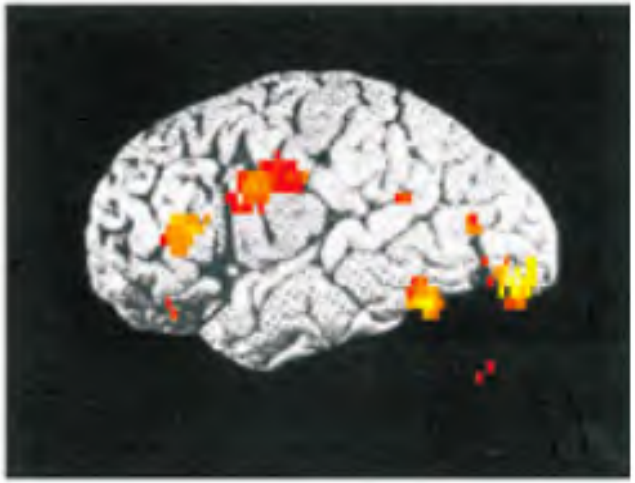


Objects- shapes

(B+C)-(A+D)

Main effect of object rec

B-A

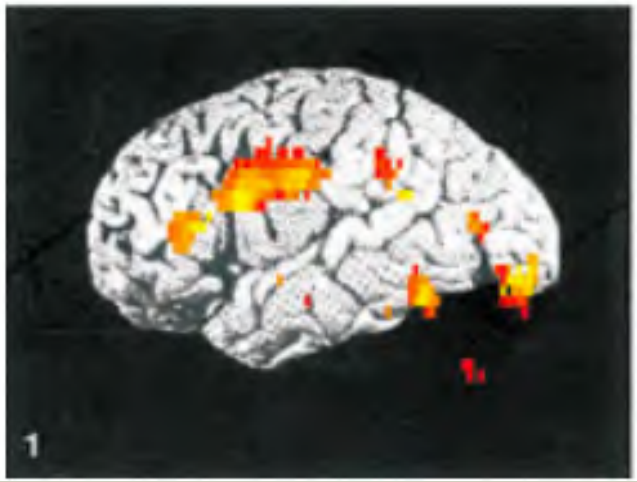


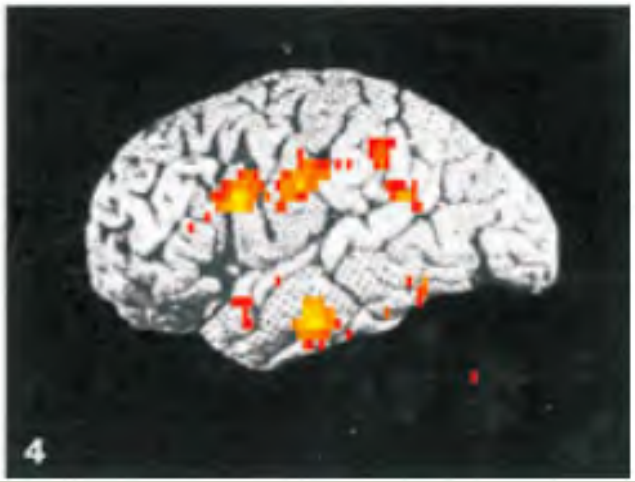
Naming vs “yes”

(D+C)-(A+B)

Main effect of phonol retr.

C-B





interaction

(C-D)-(A-B)

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

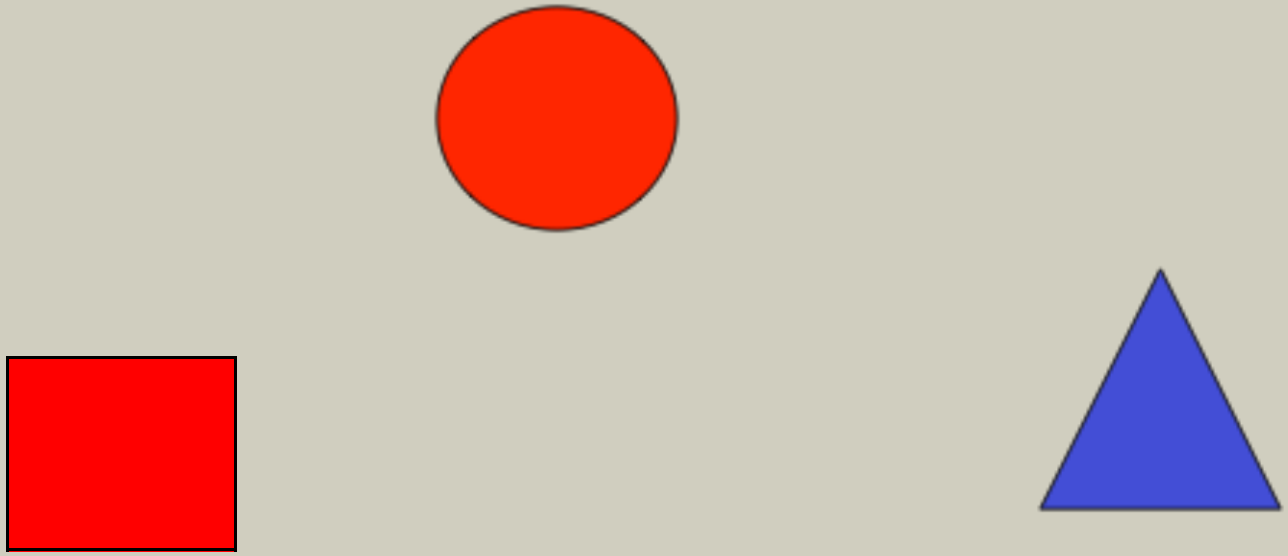
Directed Attention Models

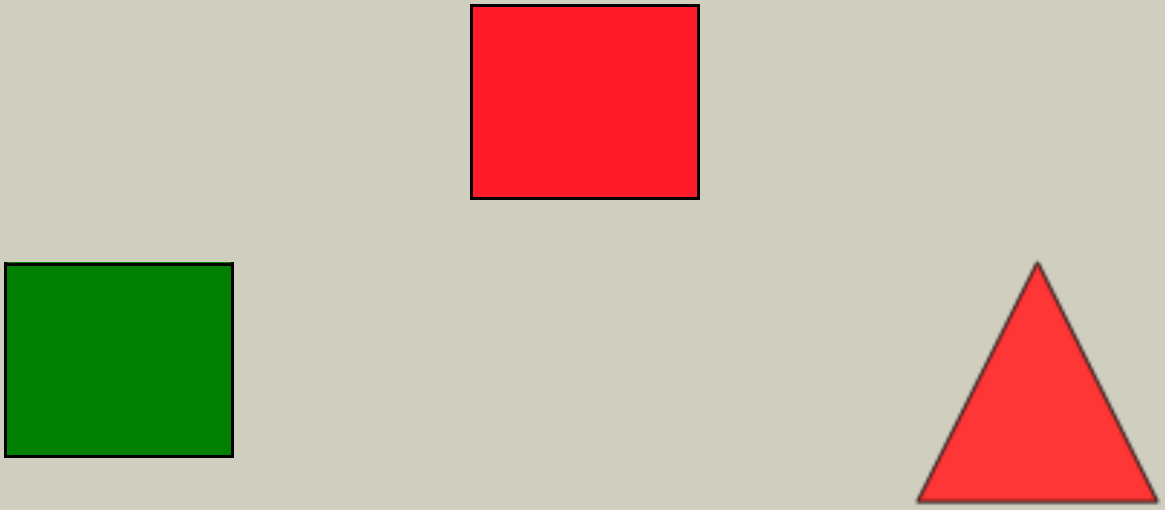
- All stimuli identical in all conditions
- Direct attention towards different features
- Eliminates the need for a control task
- Assumes that the process is modulated by selective attention

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 control tasks (multiple experimental tasks)

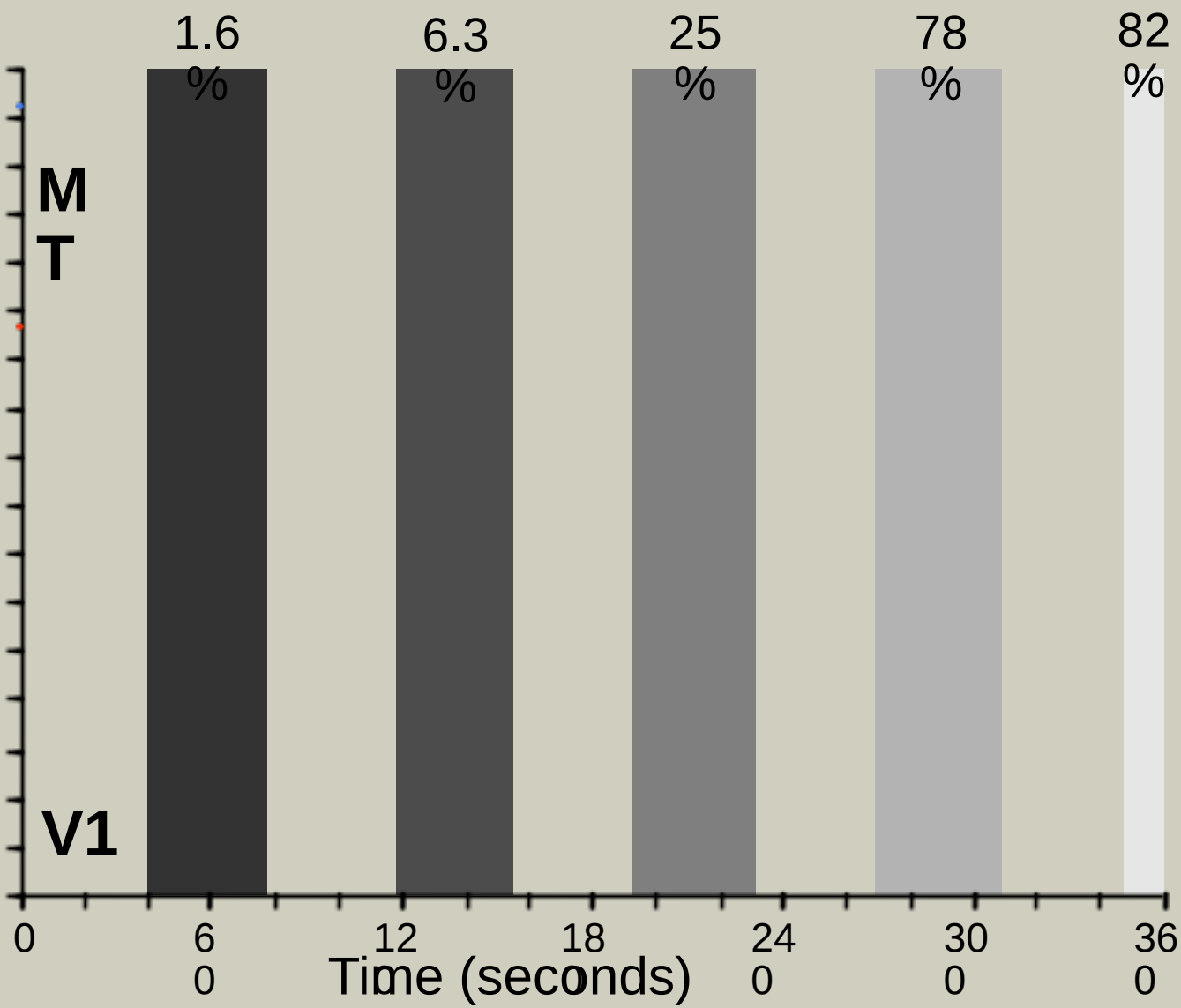
Parametric designs

- 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)

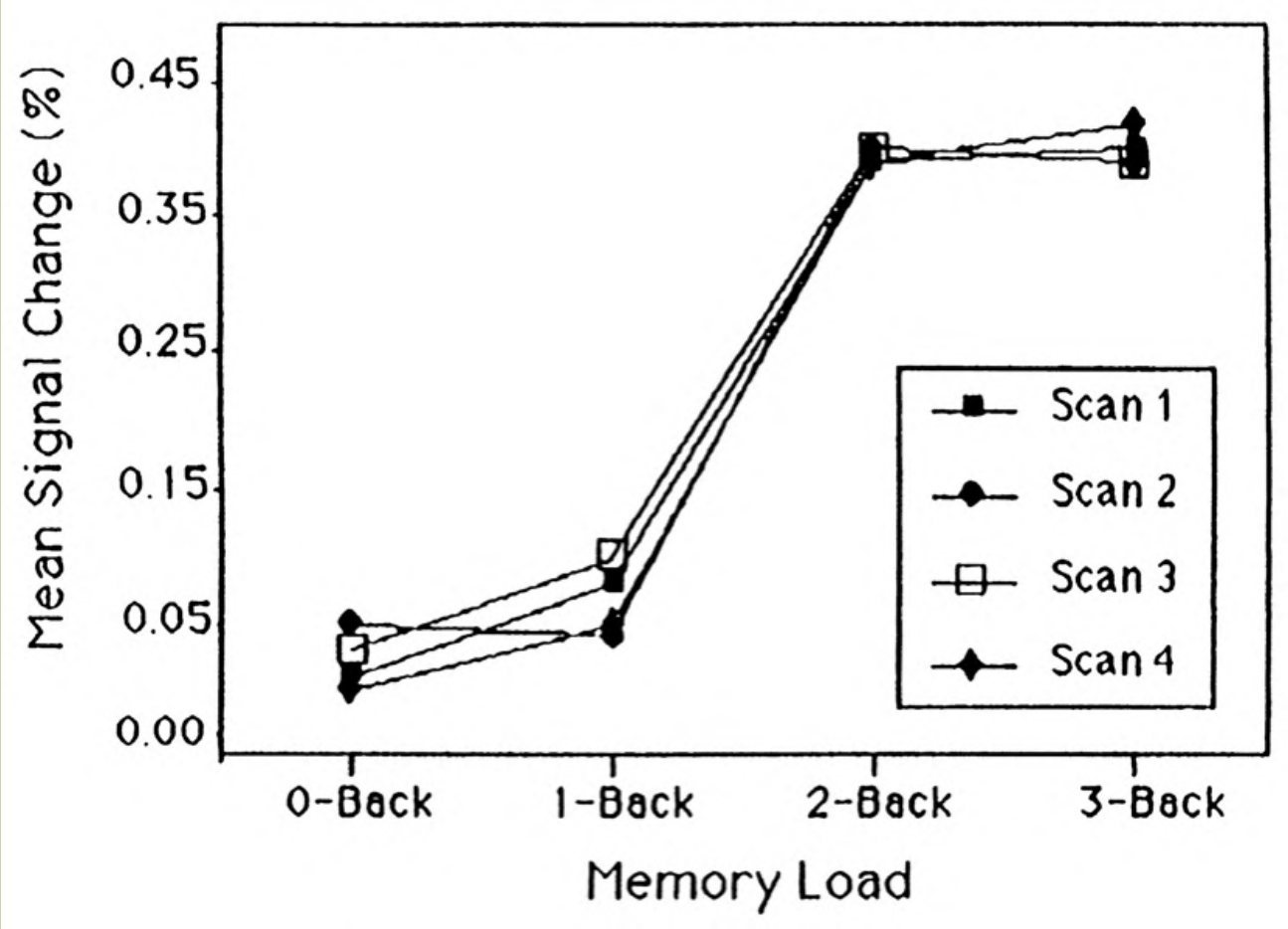


From R. Tootell

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

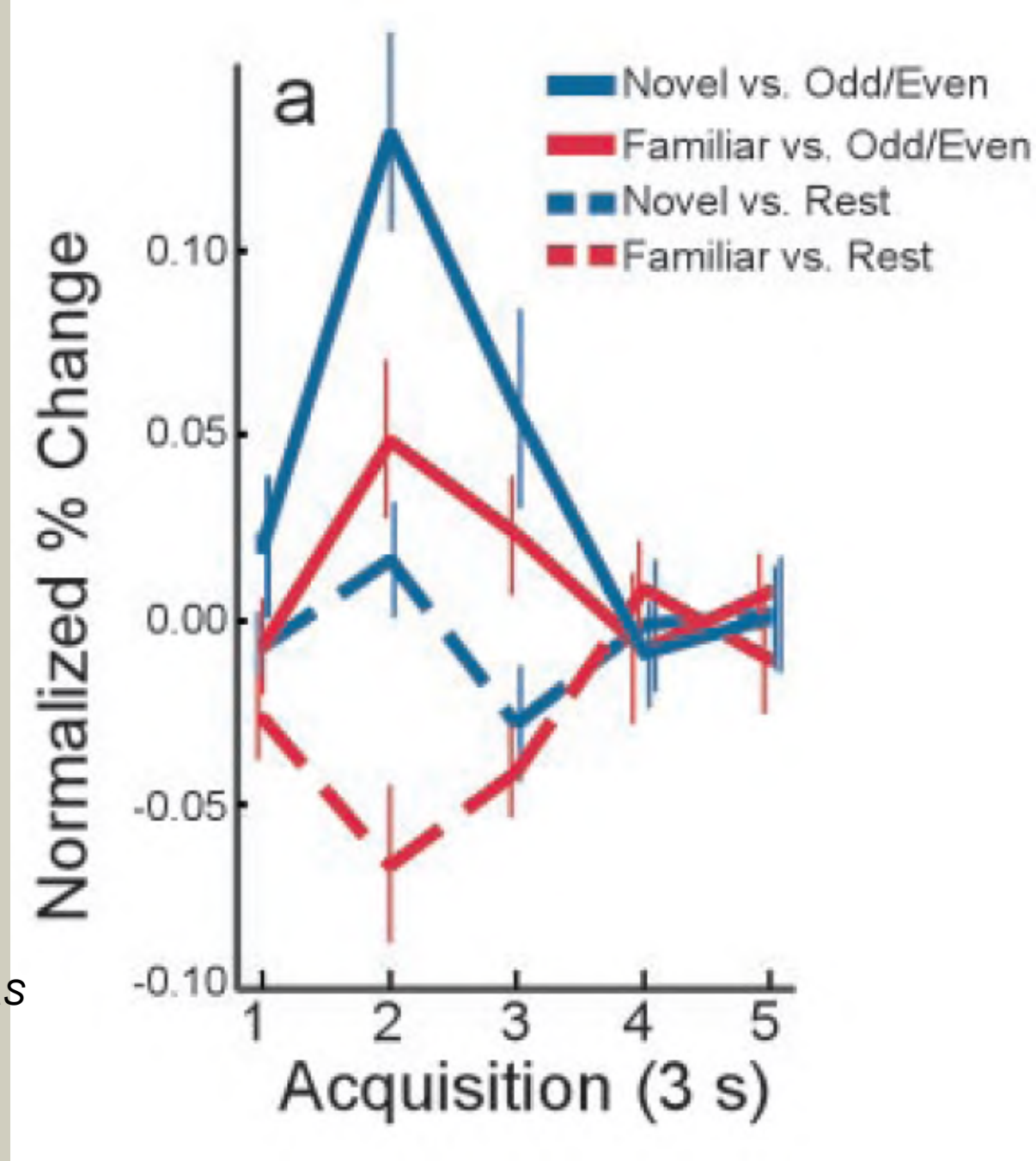
Cohen et al., 1996



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

Common in Memory paradigms



Stark et al., 2001, PNAS

Parahippocampal Cortex

Conjunction analysis (Price & Friston, 1997)

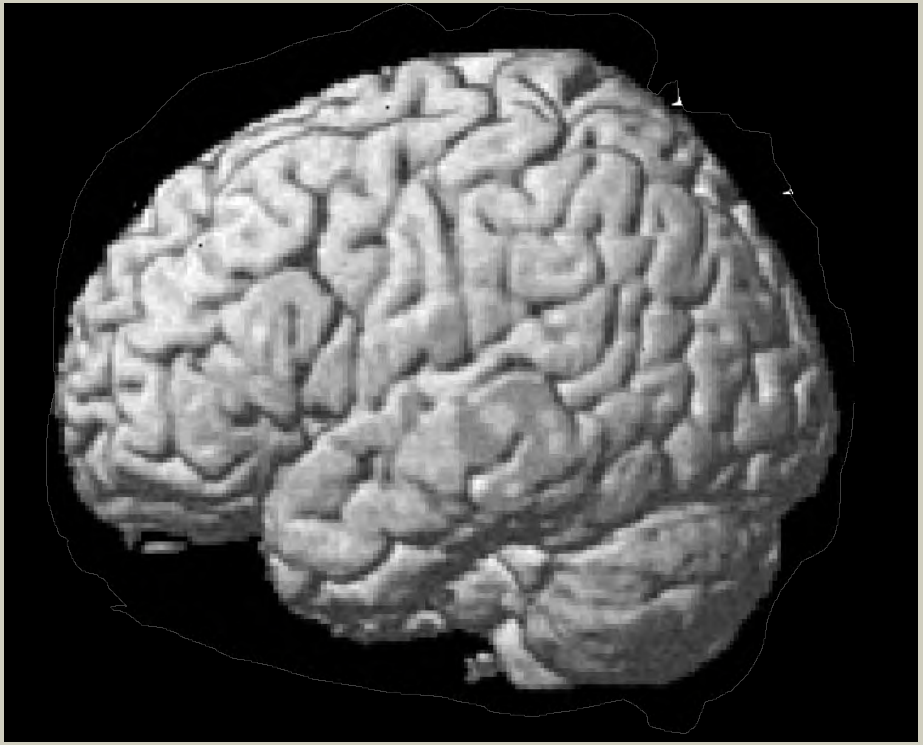
- Perform several parallel subtractions
  - Each of which isolates only the process of interest
- Find regions that show common activation across all of these

Conjunction Analysis

Ex A - Ctl

Ex B - Ctl

Ex C - Ctl

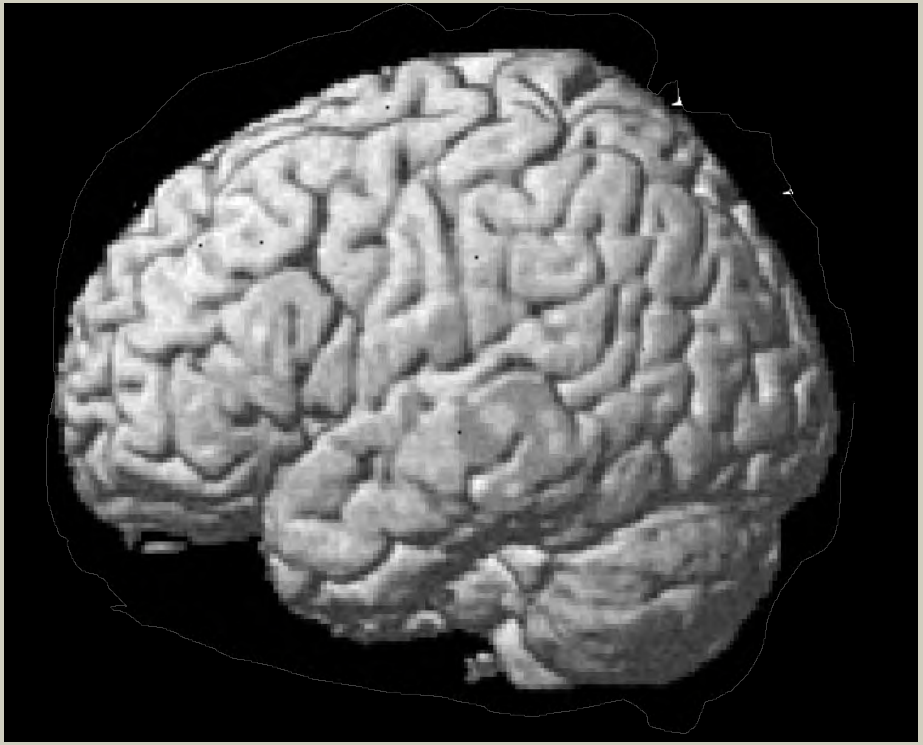


Conjunction Analysis

Ex A - Ctl

Ex B - Ctl

Ex C - Ctl

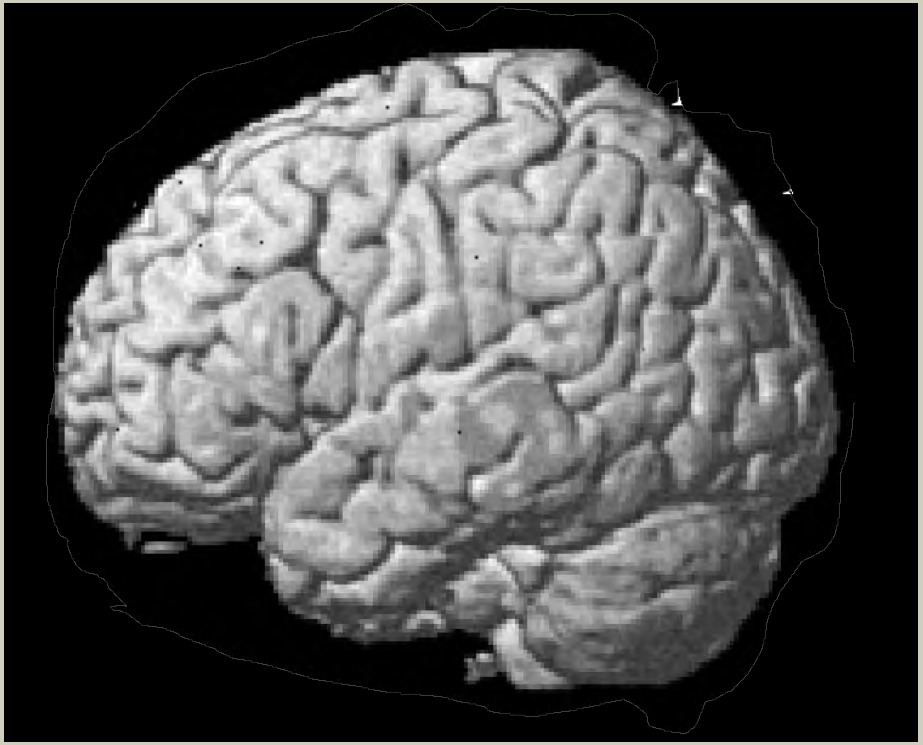


Conjunction Analysis

Ex A - Ctl

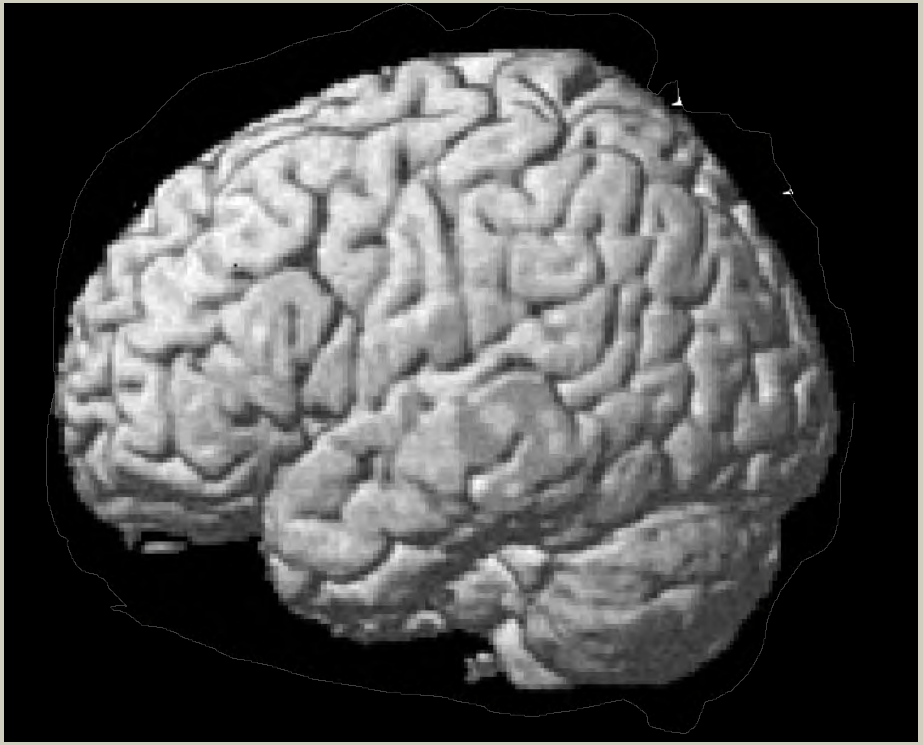
Ex B - Ctl

Ex C - Ctl

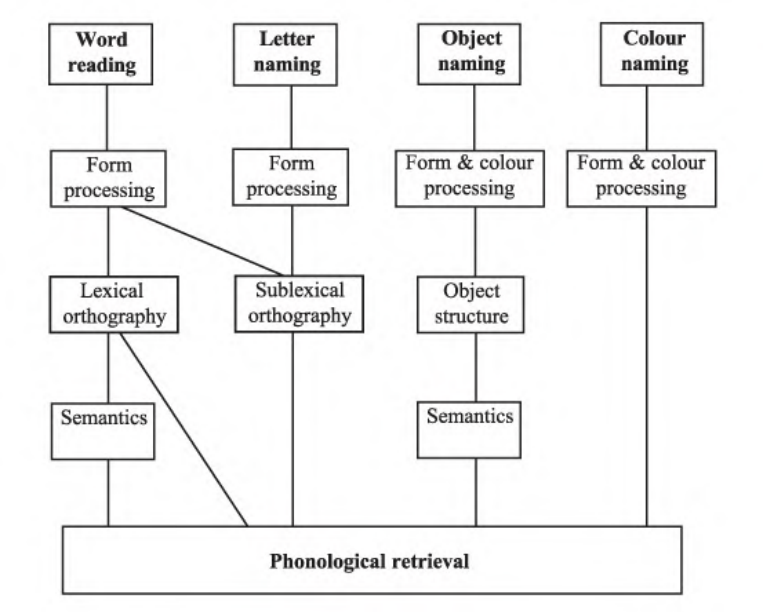


Conjunction Analysis

A AND
B AND
C



	Name (A)	Say "YES" (B)
Words:	1 badge	2 [illegible]
Letters:	3 r	4 n
Objects:	5 	6 
Colours:	7 	8 



Tasks:	Task Pair I Words A 1	Task Pair I Words B 2	Task Pair II Letters A 3	Task Pair II Letters B 4	Task Pair III Objects A 5	Task Pair III Objects B 6	Task Pair IV Colours A 7	Task Pair IV Colours B 8
Cognitive Processes								
Form processing	■	■	■	■	■	■	■	■
Colour processing					■	■	■	■
Lexical orthography	■							
Sublexical orthography	■		■					
Object structure					■	■		
Semantics	■				■	■		
Phonology	■		■		■		■	
Articulation	■	■	■	■	■	■	■	■

from Price & Friston, 1997

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

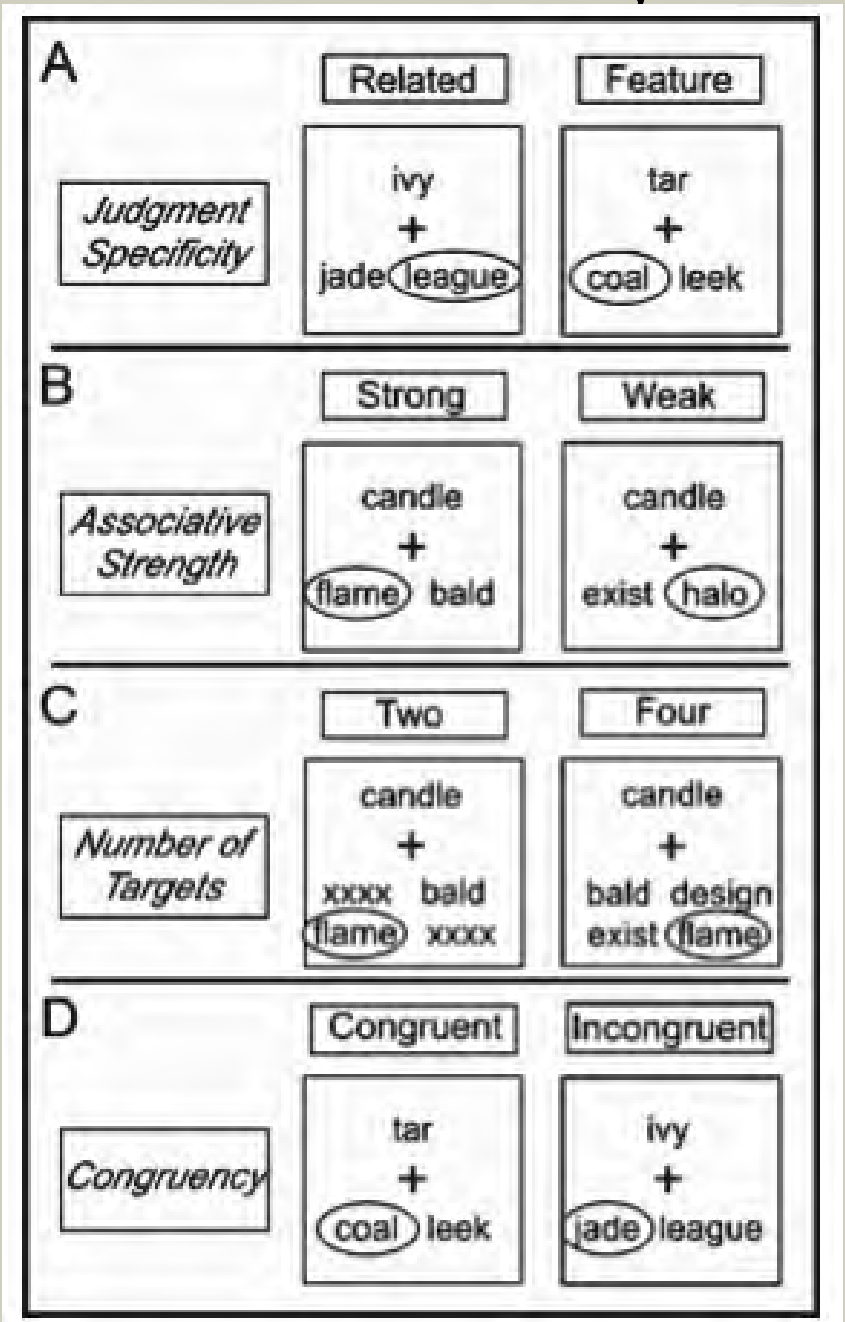
2-group designs

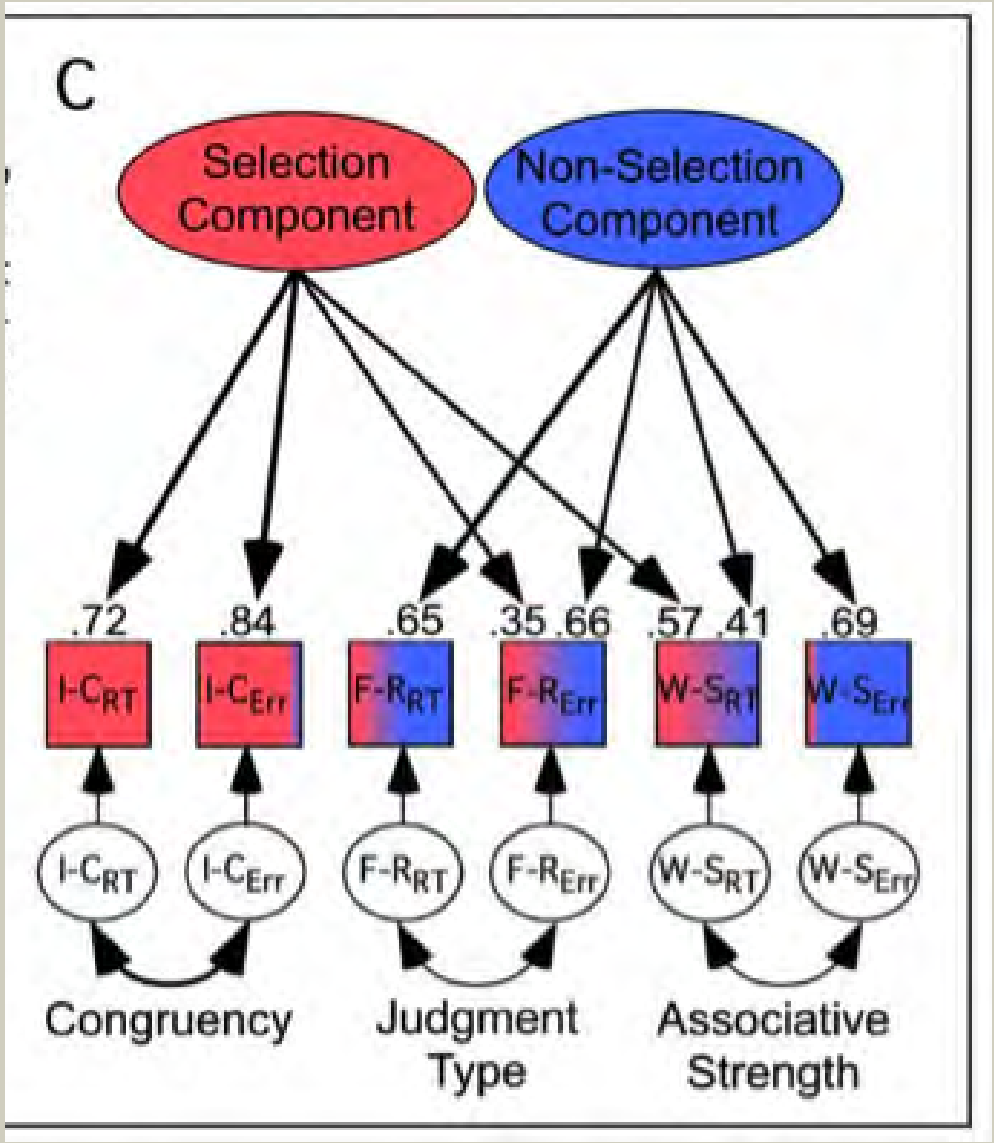
- Build on any of the prior designs
- Additional between-group comparisons
- Hypothesis sounds something like:
- *The differences between experimental and control task in my patient group differs from that difference in controls*
- Assumes baseline task performance is equal
- Assumes equal variance of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

Some cool designs

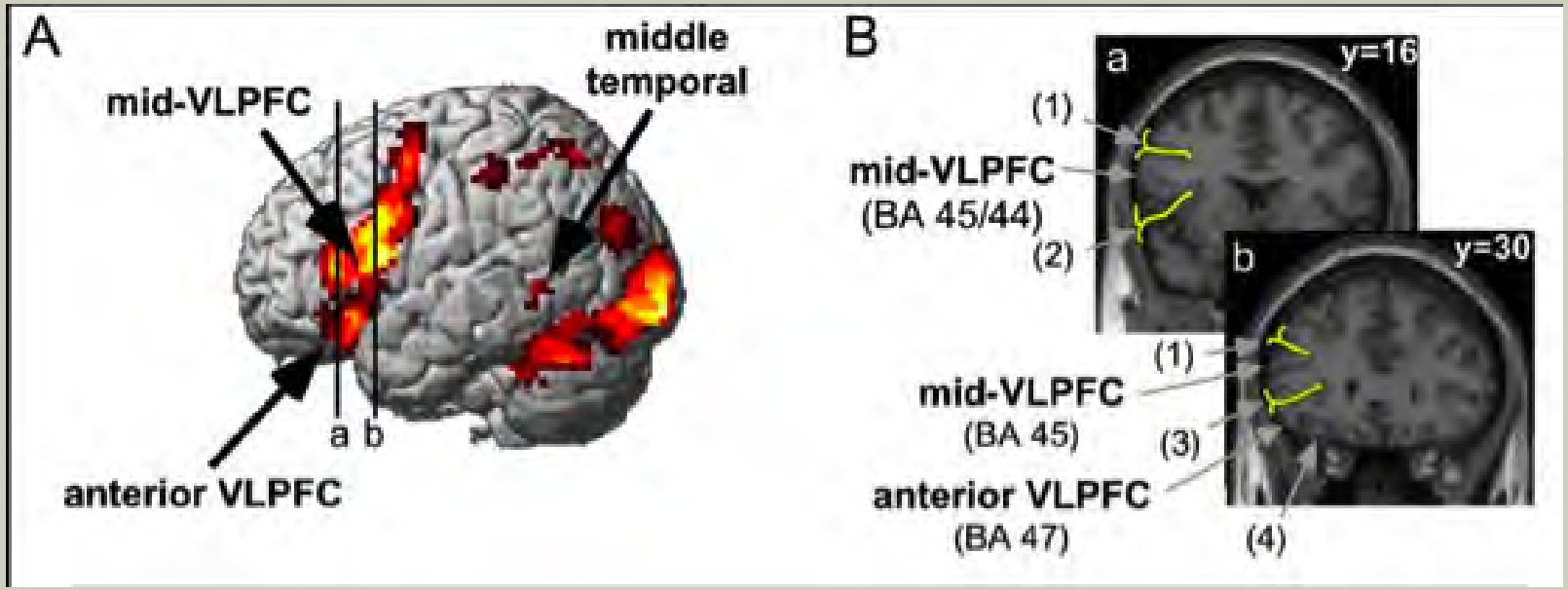
- Many of these designs can be used in various combinations and with different analysis techniques to create complex novel and cool outcomes
- Mixed, nested designs (combined event related, blocked designs) are one example

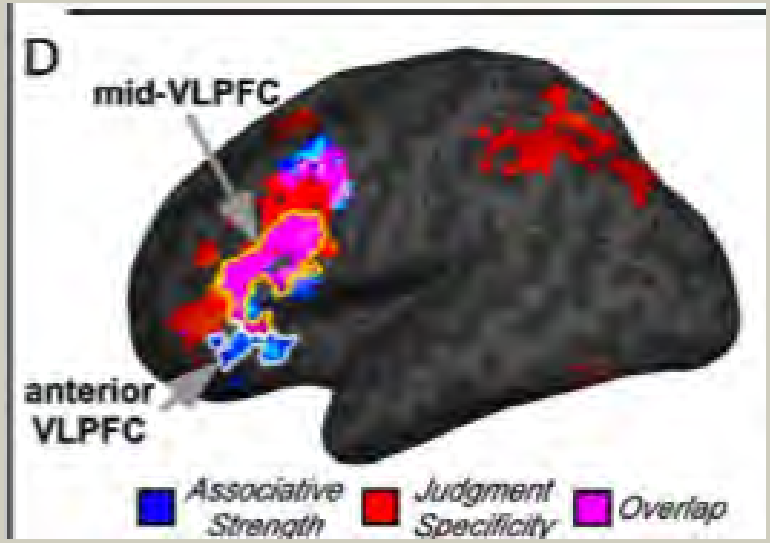
Factor-determined component classification: Badre, Poldrack et al 2005





IFG dissociations





Badre, Poldrack etc 2005

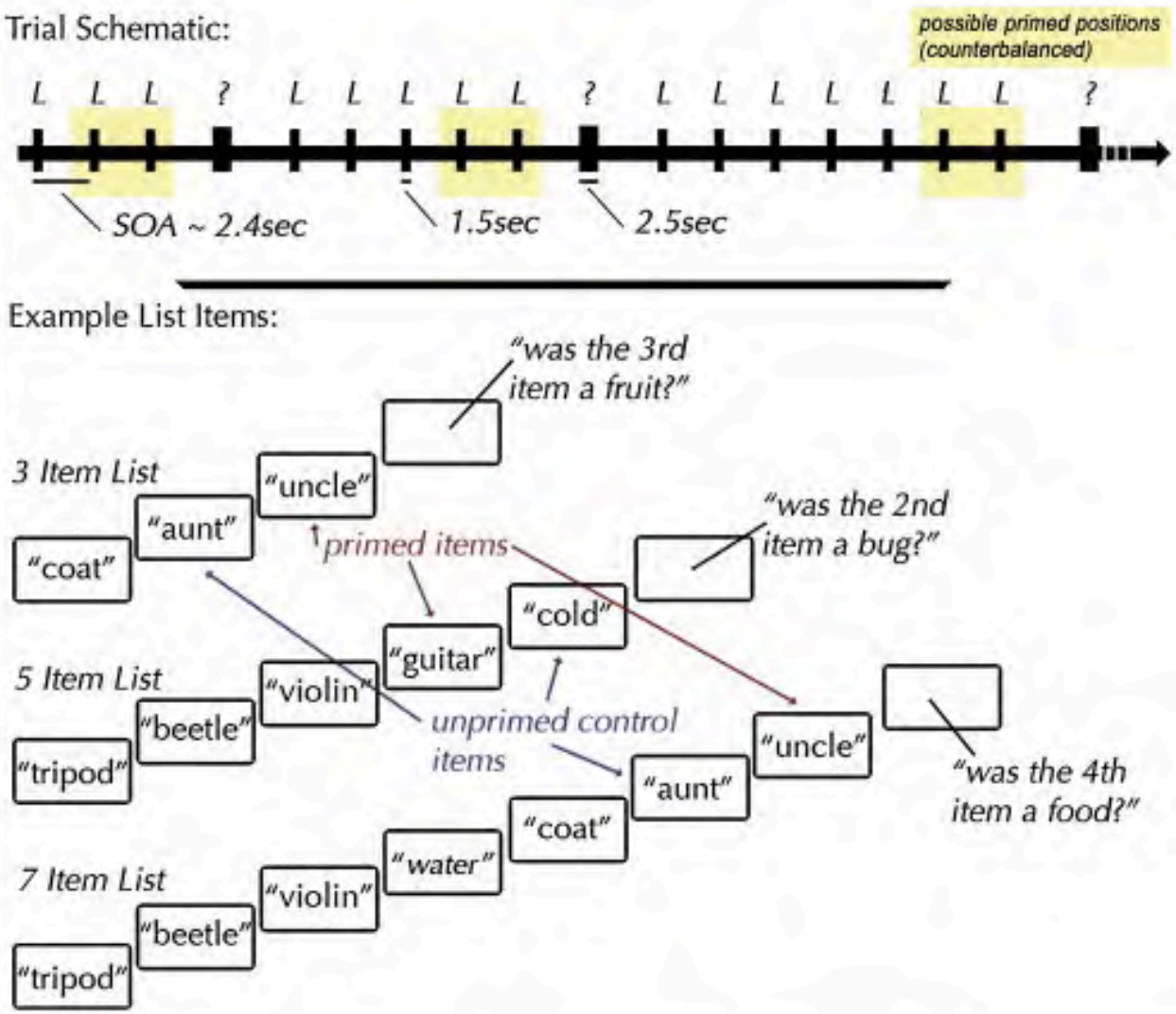


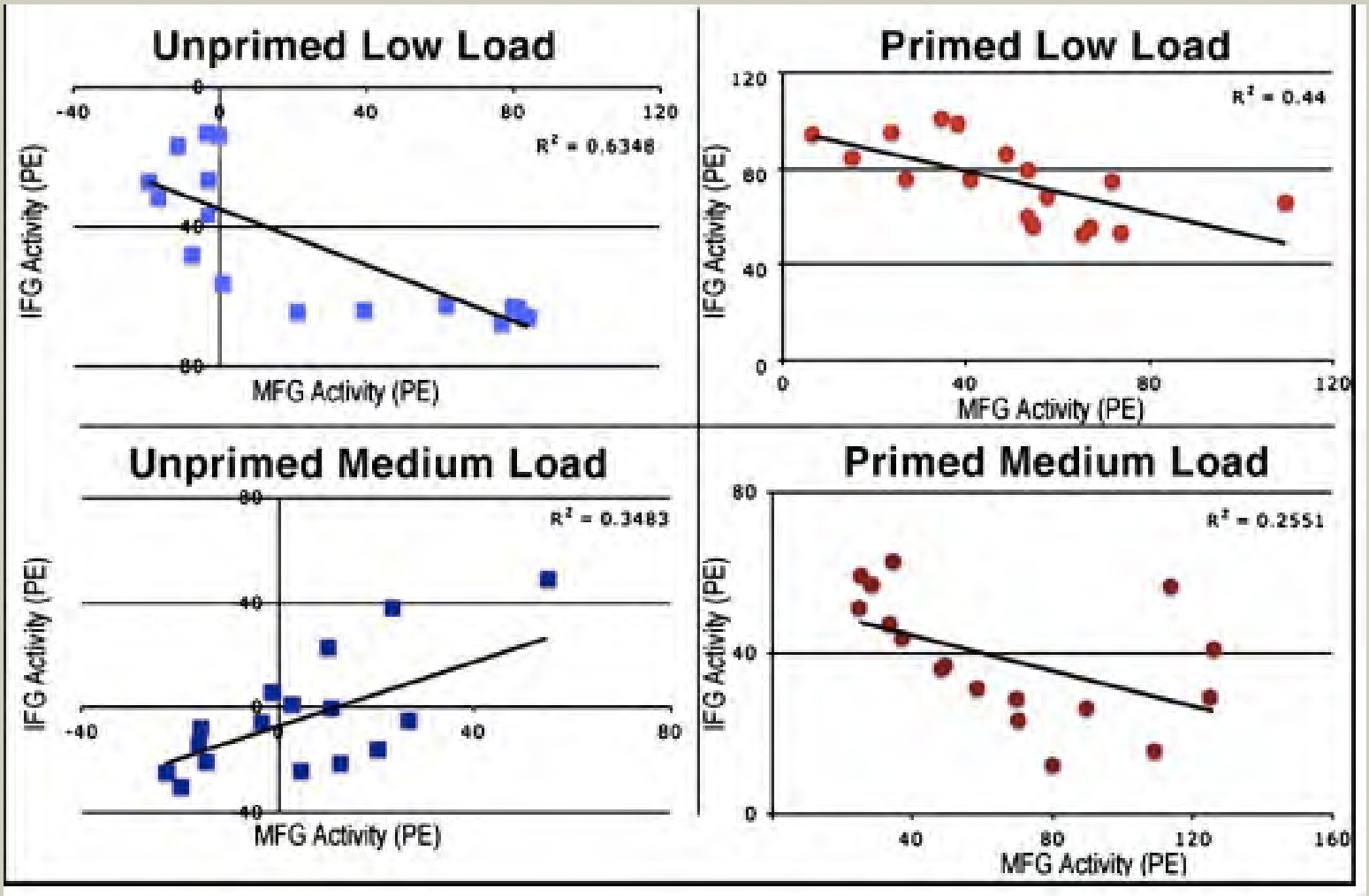
Fig. 1.

Task schematic. Subjects saw a serially presented list and then responded to a question about one list item. Top panel is a trial schematic. Tick marks represent either list items (L) or probe questions (?). Lists varied in length, either 3, 5 or 7. Highlighted regions represent possible locations where priming target could occur. Bottom panel shows sample trials for 3, 5 and 7 item lists.

Sabb et al, JOCN

Combined event related, parametric priming adaptation design to determine if working memory load limited semantic processing

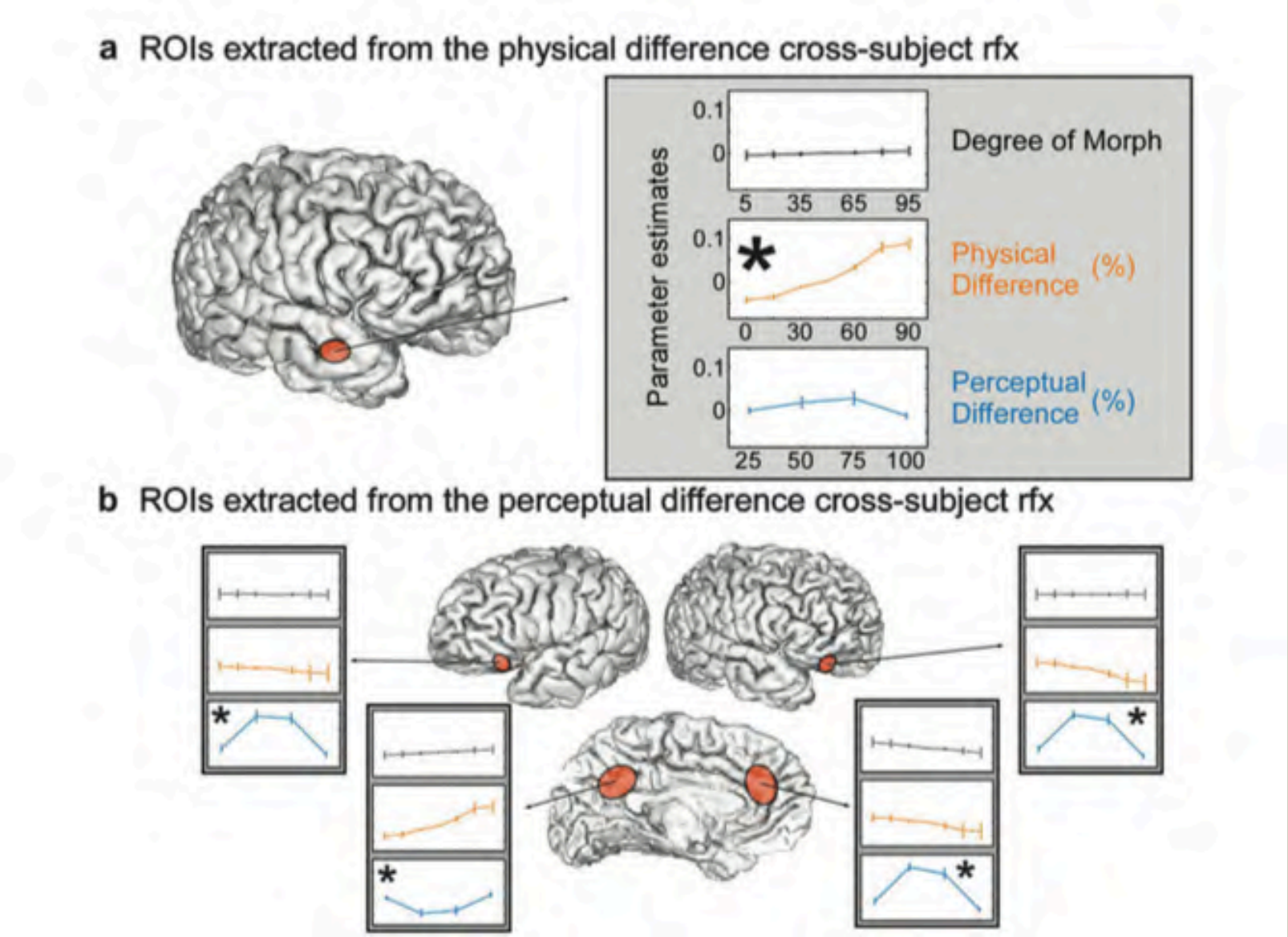
Differential coupling between OFC and DLPFC under low and high WM conditions



Charest et al, Cerebral Cortex, 2012

Continuous carryover design (adaptation, with parametric manipulation of stimuli- morphing male voice to female) to identify processes involved in voice-gender identification

Differentiated responses to physical attributes of stimuli to perceptual one (categorized as male/female)



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
- Have a hypothesis before you begin
- Multiple “baseline” conditions help interpretation
- Look at your data at every step as you go