Experimental Design for Brain Imaging I

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fMRI experimental design: A basic plan

Define mental process to examine

↘

Define tasks to manipulate that process

↘

Measure fMRI data during tasks

↘

Compare fMRI data between tasks

Replace "fMRI data" with "RT" and you have cognitive psychology!

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
- Challenge: Know your assumptions; choose the design that best answers your question, minimizes your assumptions, and allows you to test your assumptions

General Design approaches

- Subtraction-based designs
- Factorial Designs
- Parametric Designs
- Selective Attention Designs
- Adaptation Designs
- Conjunction approaches
- Weird stuff

General Design approaches

- Subtraction-based designs
  - Multi-level hierarchical subtraction
  - Simple subtraction and directionality
  - Common baselines and parallel comparisons
  - Tailored baselines

Experimental Example: semantic processing

Experimental Question: Language stimuli can enter the brain through various modalities: auditory, printed word, meaningful pictures.

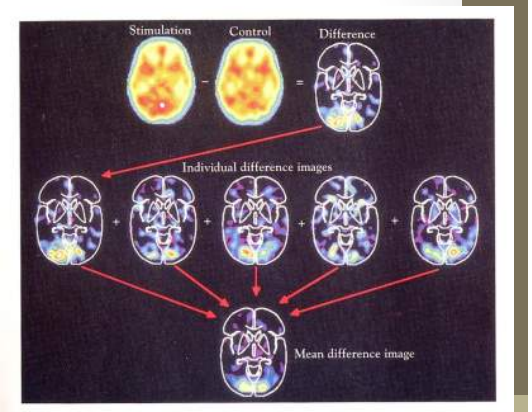
What areas of the brain are essential for language (semantic) processing, independent of input modality, and unrelated to other factors such as motor output? What specific processes take place during language performance?

HOUSE

"HOUSE"

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

Hierarchical subtraction

example from Petersen, 1991

Design: Subtract out sensory and motor aspects of language from higher order semantic tasks using hierarchically based subtractions

- Rest Control -
- Auditory words or Visual Word (passive presentation) -
- Reading or repeating words vs passive words: motor areas -
- Generating words vs. repeating: semantic (language) areas

} Sensory

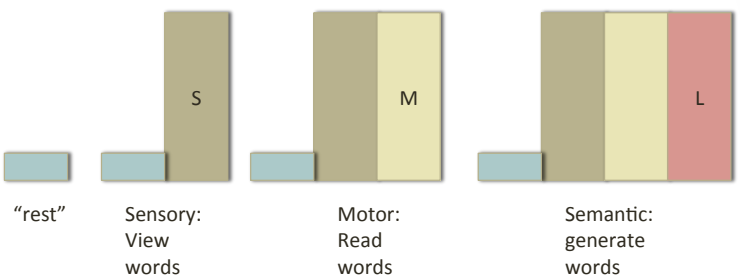
} Motor

} Semantic

The pure insertion assumption

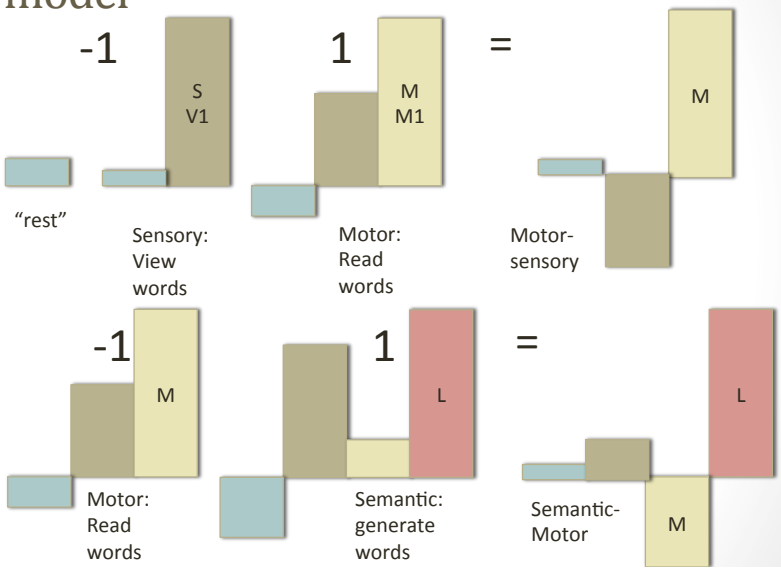
- Subtraction requires a strong assumption of "pure insertion"
- *Insertion of a single cognitive process does not affect any of the other processes (no interactions)*
- "Controlled" variables do not change as you add processes (move "up" the hierarchy)
  - Eg, Neural processes involved in reading words out loud are identical to those in reading silently, plus motor
  - PI must hold at both neural and cognitive levels

Pure insertion in a hierarchical model



In hierarchical subtraction models, you pile up the pure insertion assumptions with each additional hierarchical level!

Failure of pure insertion in a hierarchical model



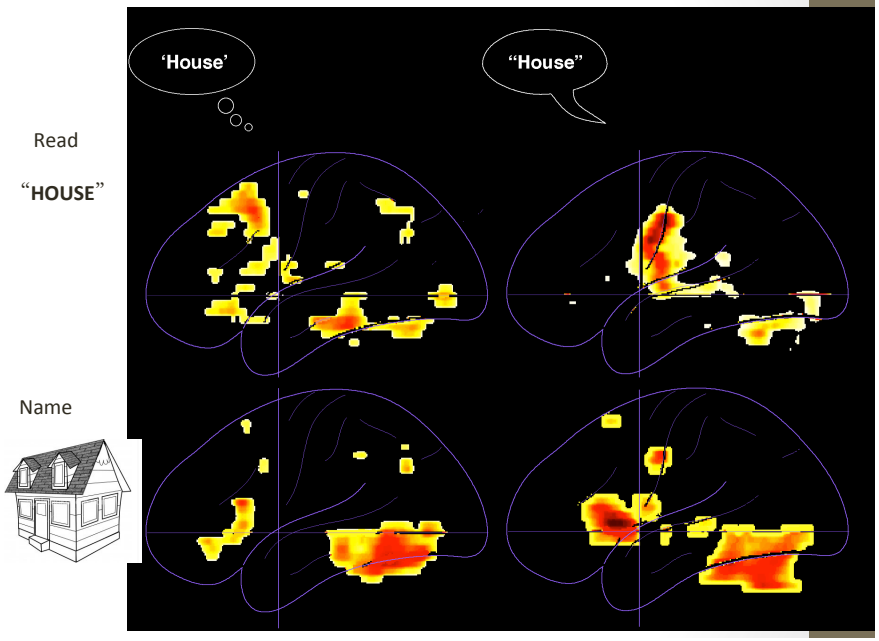
Common Baseline

Is there evidence for pure insertion: Does reading words aloud add motor areas without changing silent reading areas?

- 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

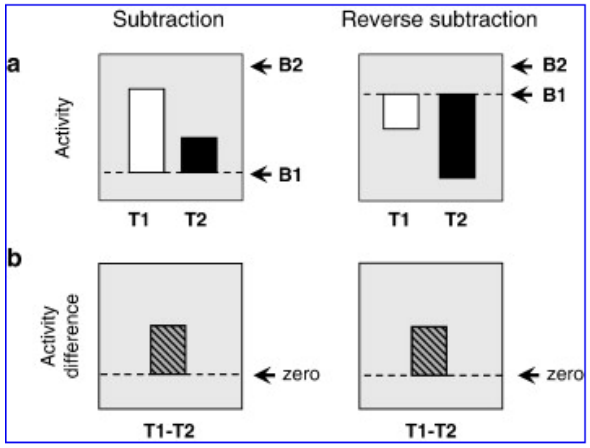
Ex A → Control ← Ex B

Silent reading → Rest ← Oral Reading



Simple subtraction 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)
- Often assume (mistakenly) that differences are due to increases in one condition- that which is the "higher order" task or the experiment (vs. control) task



From Morcom and Fletcher, NeuroImage, 2006

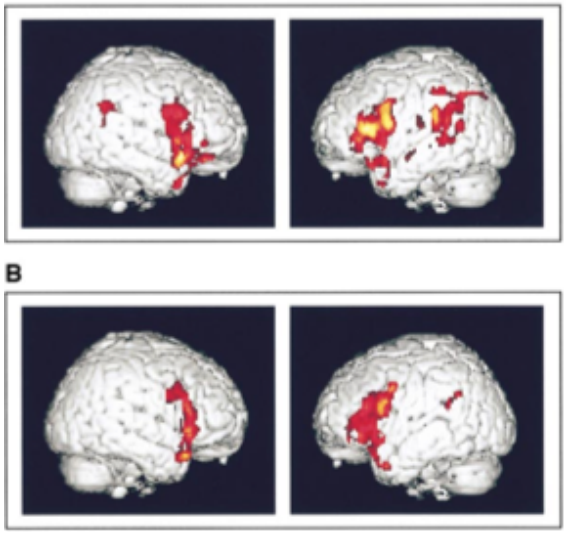
Assuming no hierarchy: Parallel Comparisons

- 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**

Ex B > Ex A	**Hear Words** > **See Words**	See Words > Speak Words
Ex A > Ex B	**See Words** > **Hear Words**	Speak Words > See Words

Dapretto et al: Semantic vs. Syntactic Processing

Common Baseline comparison



Word order change

The city is west of the school

West of the school is the city

Word change

The city is west of the school

The town is west of the school

Dapretto et al: Semantic vs. Syntactic Processing

Parallel comparison

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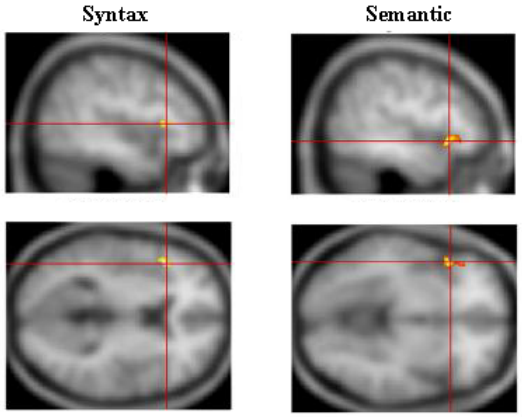

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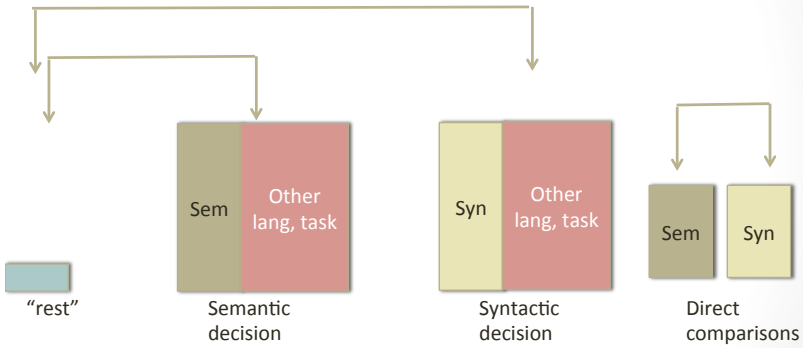
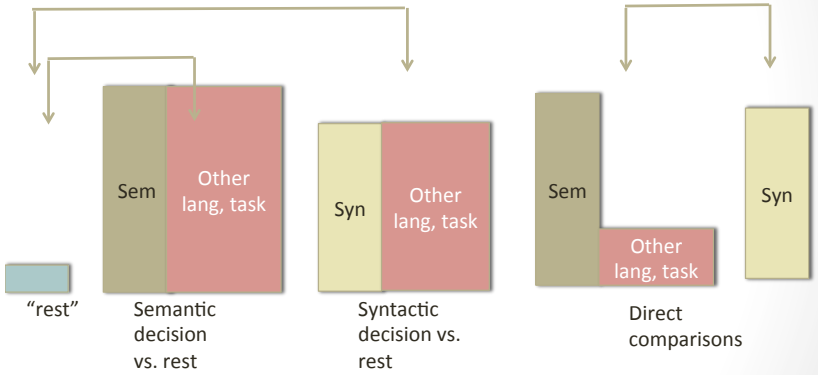
Dapretto and Bookheimer, Neuron, 1999

Common baseline and Parallel comparisons



But one task could be harder…..

---Assumes similar psychometric properties of tasks

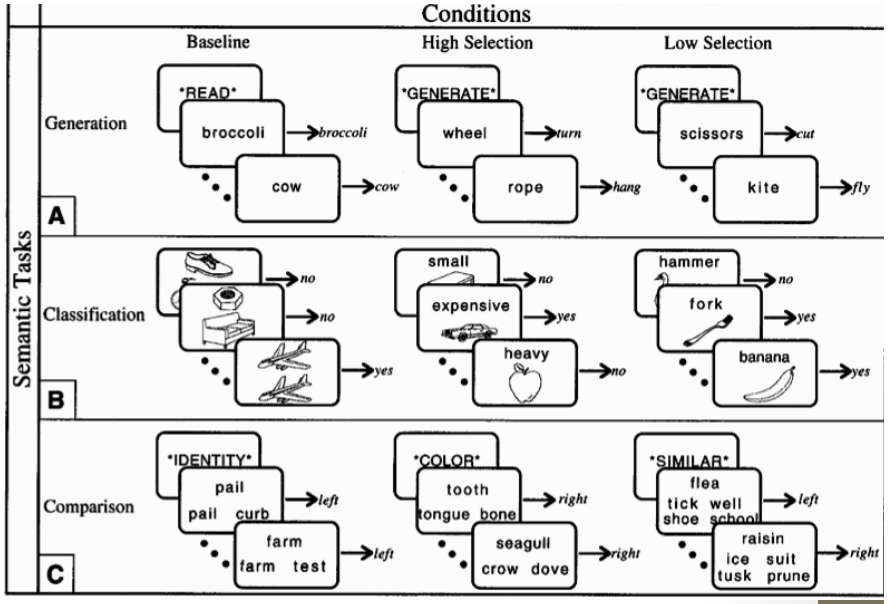


Tailored baseline

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*

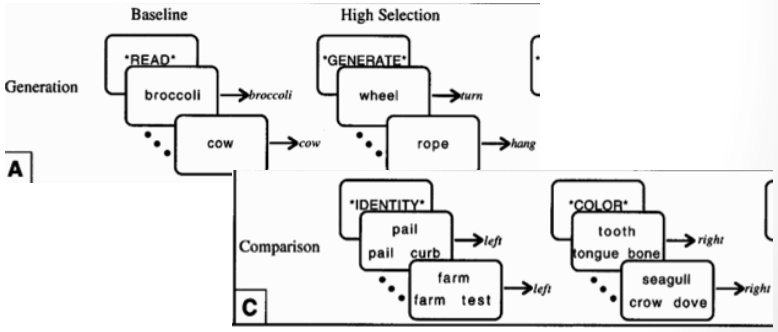
- Example study (Thomspon-Schill, PNAS 1997): Do frontal areas implicated in semantic processing really involve semantics, or are they instead important for response selection (independent of task)
- Use 3 different tasks: generation, classification, and comparison; each has its own control, each as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



Thompson-Schill et al PNAS 1997

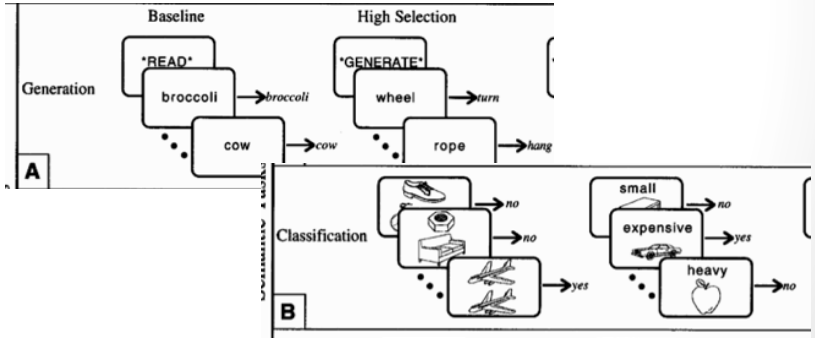
Tailored baseline

- Assumes baseline tasks control for (sensory input) equally
- reading a word controls for generating an associate to a word, as well as matching a word controls for matching a property



Tailored baseline

- Assumes similar psychometric properties of both experimental and both control tasks
- The distribution of behavior and its neural responses (magnitude, RT, sd, etc) for high selection generation compared to reading : is the same as that for high selection classification compared to the control
- Need very extensive behavioral testing



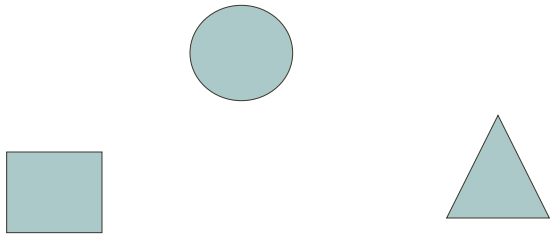
Factorial design

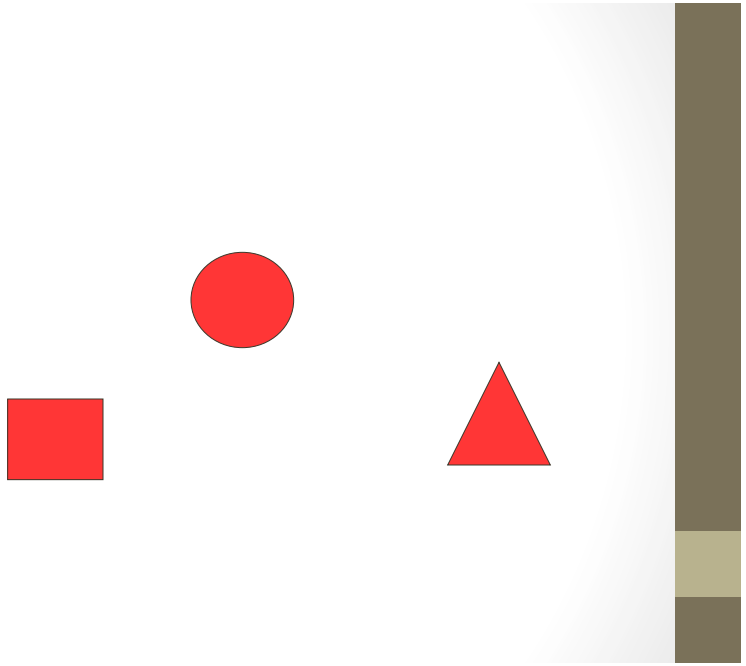
- A factorial design involves multiple concurrent subtractions
- Allows for testing of interactions between components
- Still requires pure insertion assumption and task decomposition
  - But additivity can be tested for the specific factors that are manipulated

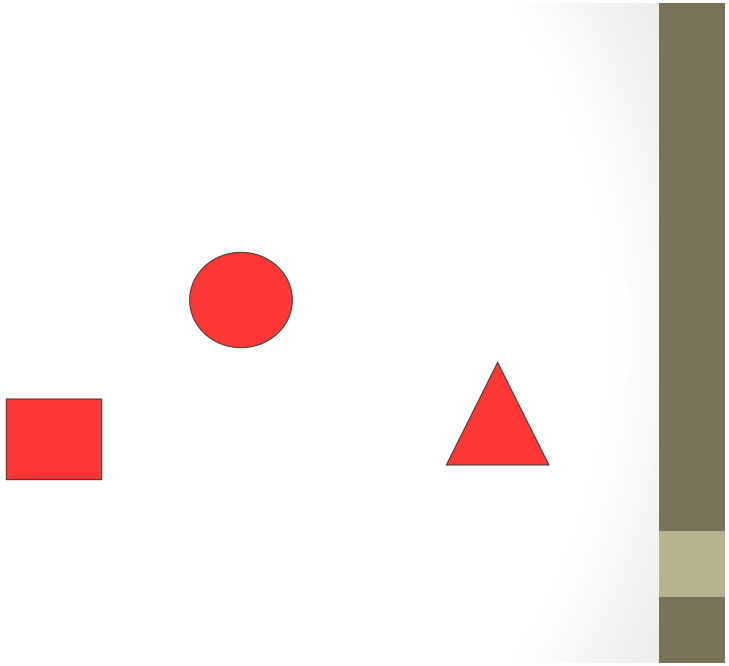
Directed Attention Models

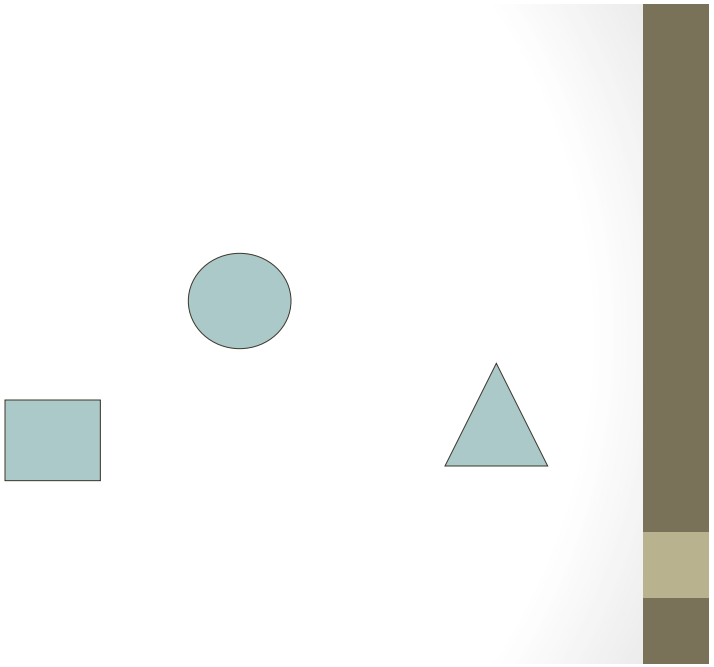
- All stimuli identical in all conditions
- Direct attention towards different features
- Implicit or explicit
- Assumes process is modified by directed attention
- Assumes passive processing does not capture your variable of interest

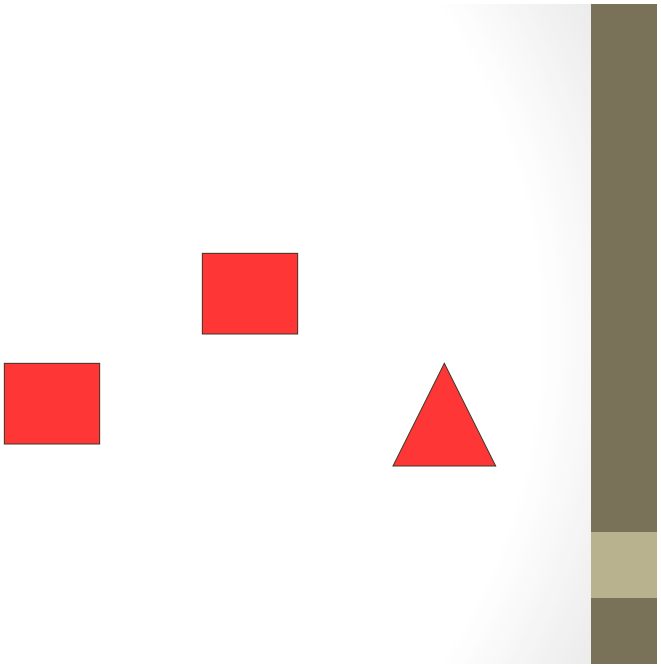
EG Corbetta et al











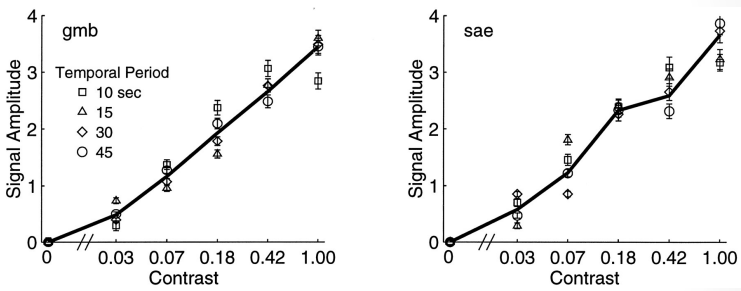
Selective attention

- 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
- Assumes your process of interest is modified by directed attention (often true, not always)
- Can be done explicitly or implicitly (You can change a factor that does not change instructions)
  - Read words; some may be high, others low imagery

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

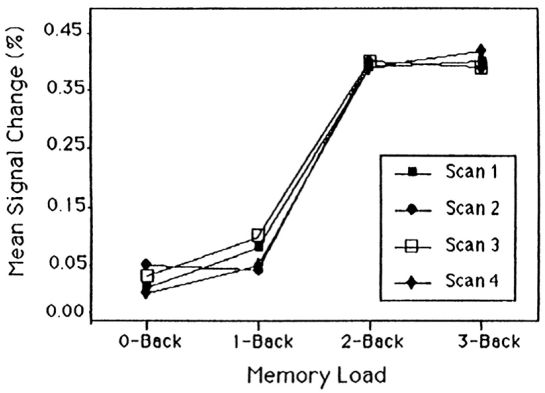
Boynton et al., 1996



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



0 and 1-back do not require WM; 2 does; step function with a qualitative change in process

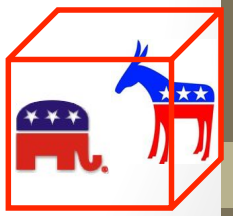
Priming/adaptation designs

- 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?

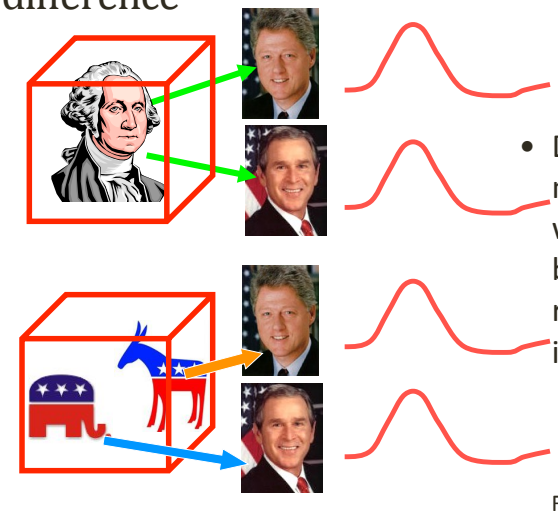
- A voxel containing neurons that respond to all politicians, irrespective of party



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

From R. Raizada

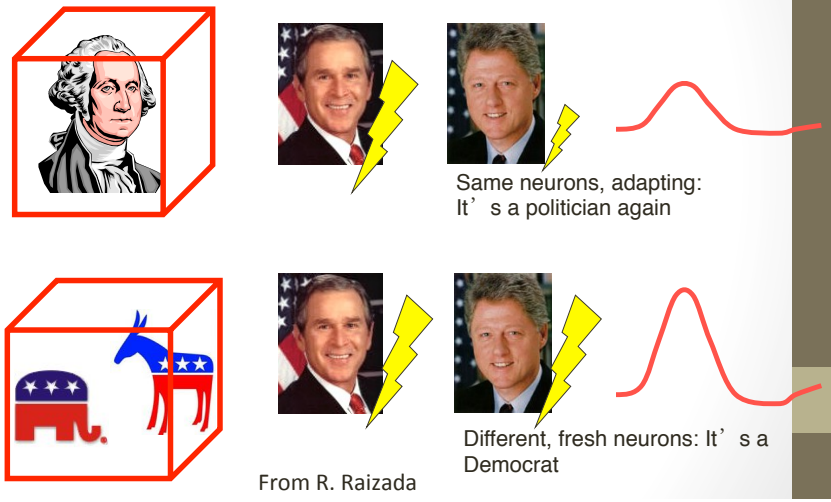
Responses to individual stimuli do not show whether neurons can tell the difference



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

From R. Raizada

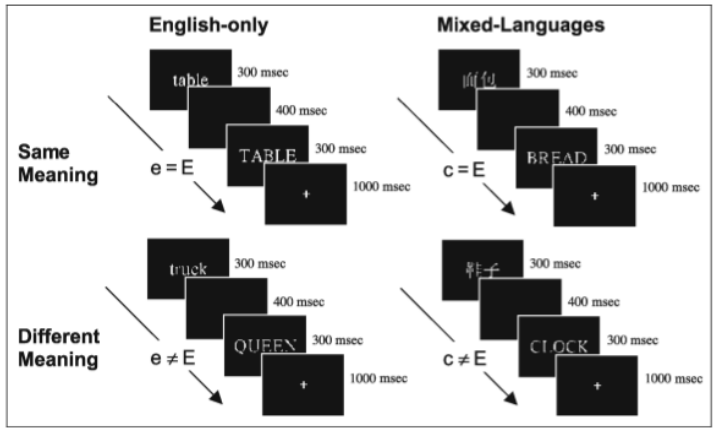
Neural adaptation to repeated stimuli does show the difference:
What counts as repetition for neurons in a voxel?



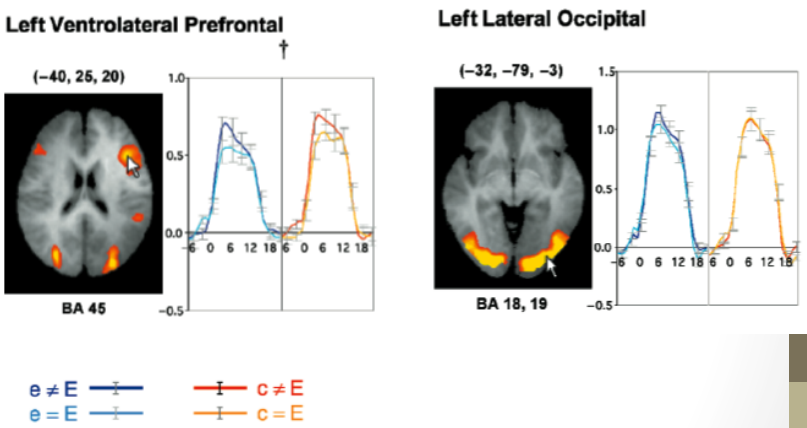
From R. Raizada

Adaptation in bilingual subjects

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



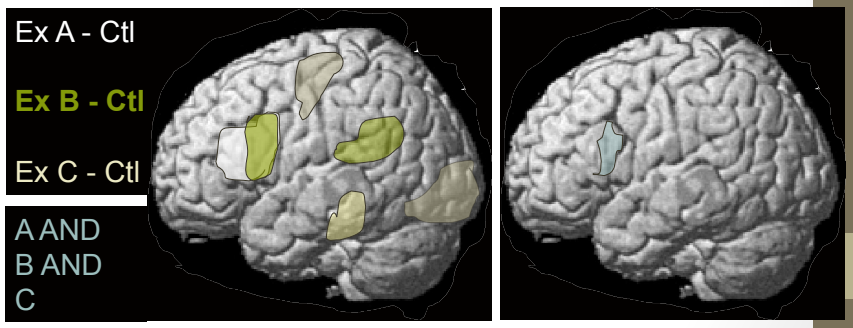
Chee et al 2003

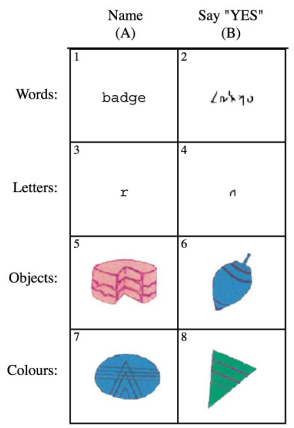


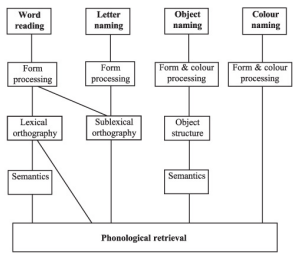
Main effect for meaning (adaptation) in LIFG, not LOcc

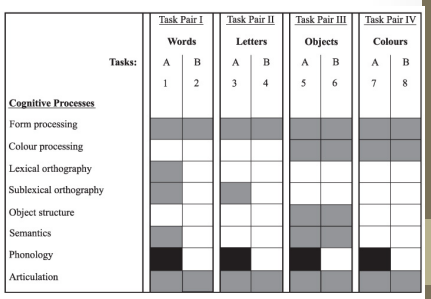
Conjunction analysis (Price & Friston, 1997)

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



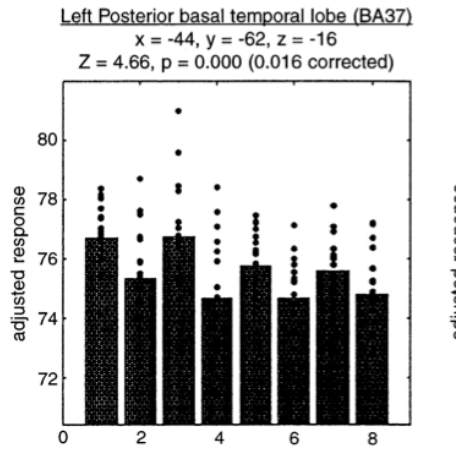






from Price & Friston, 1997

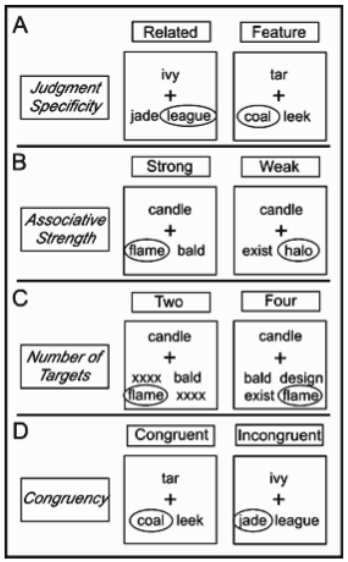
BTLA- all tasks involving accessing phonology

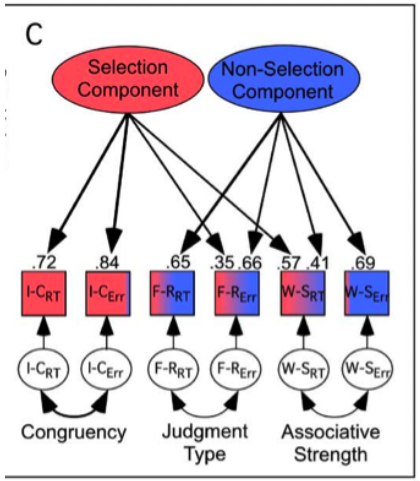


Problems with conjunction analysis (Caplan & Moo, 2003)

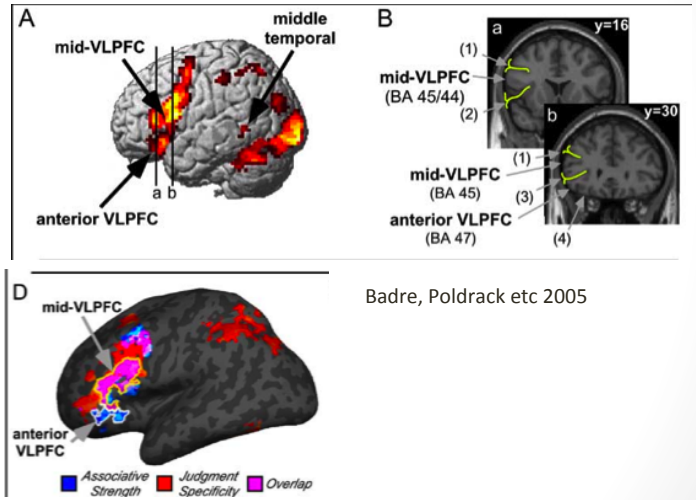
- Many assumptions about what processes are involved
- Implicit processing
  - Subjects may engage processes that are not necessary for the task- does not measure magnitude differences
- Interactions between processing stages
  - Conjunction only gets rid of interactions if they do not activate the same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

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





IFG dissociations



Badre, Poldrack etc 2005

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
- What if one group cannot perform the task well?
  - Eg: dyslexia: give a non-word reading task

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**

Summary

- No design is perfect
- Use that which is most consistent with your specific research question
- Multiple "baseline" conditions help interpretation
- Behavioral data is extremely helpful in supporting many assumptions and preventing critical errors
- Beware of your assumptions! all designs make assumptions that are not fully verifiable; know them!
- Freely admit your design limitations